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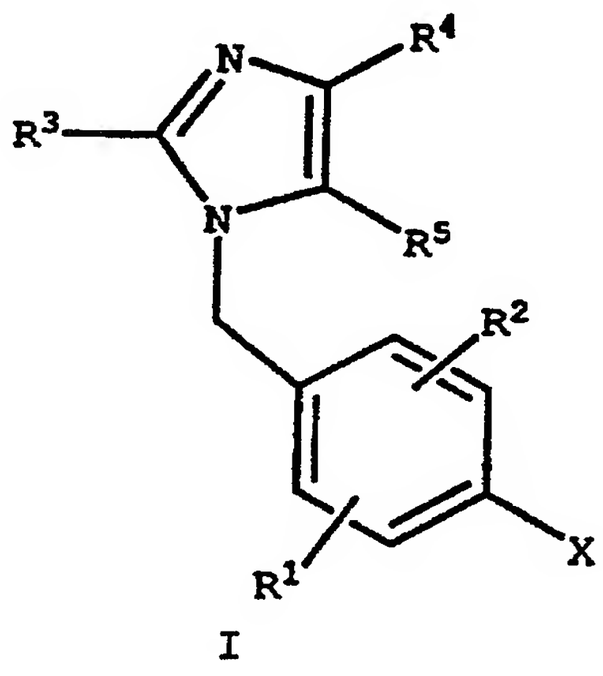
C2C CAA CBG CKK CQZ CSB CSC CTA CUK CZD C1173 C1176 C1177 C1410 C1420 C1464 C213 C214 C215 C22Y C220 C221 C222 C226 C246 C248 C25Y C250 C252 C258 C267 C28X C280 C30Y C31Y C311 C313 C337 C34Y C342 C35Y C350 C351 C355 C36Y C360 C361 C364 C366 C367 C368 C37X C37Y C373 C385 C387 C43X C510 C514 C52X C52Y C520 C574 C614 C62X C623 C624 C625 C628 C638 C65X C652 C668 C675 C678 C694 C695 C699 C77X C77Y C80Y C802
U1S S2415

(56) Documents Cited
DE 004032522 A
J. Med.Chem.,35(14),2658-67,(1992),Ho-Shen Lin et al. J.Chinese Chem. Soc., 40, 273-82,(1993)Ho-Shen Lin et al.

(58) Field of Search
INT CL[5] C07D 233/54 471/04
ONLINE DATABASES: CAS-ONLINE, EDOC

(54) Angiotensin-11 receptor blocking cycloalkylbenzylimidazoles

(57) Novel cycloalkylbenzylimidazoles of Formula (I),



I

where X is a cycloalkenyl group substitutes at the alpha position by a carboxyl or tetrazolyl group.
These compounds are useful angiotensin II antagonists.

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TITLE

ANGIOTENSIN-II RECEPTOR BLOCKING CYCLOALKYLBENZYLIMIDAZOLES

FIELD OF THE INVENTION

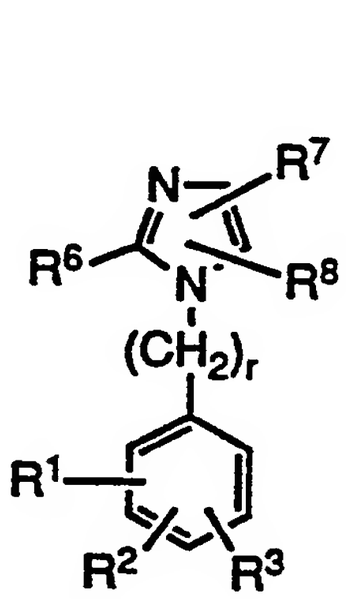
This invention relates to novel cycloalkylbenzylimidazoles. The invention also relates to pharmaceutical compositions containing these novel imidazoles and pharmaceutical methods using them, alone and in conjugation with other drugs, especially diuretics, angiotensin converting enzyme (ACE) inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDS).

BACKGROUND OF THE INVENTION

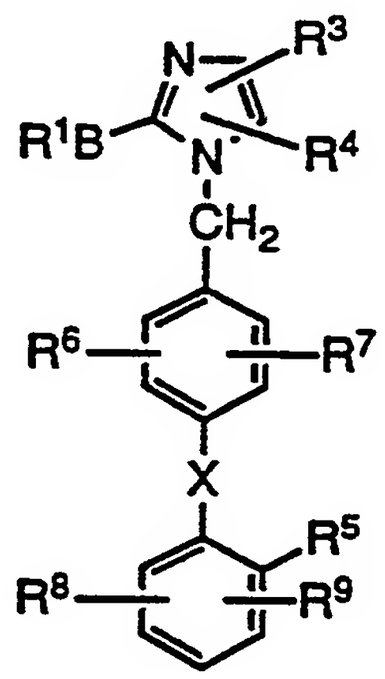
The compounds of this invention inhibit the action of the hormone angiotensin II (AII) and are useful therefore in alleviating angiotensin induced hypertension. The enzyme renin acts on a blood plasma α2-globulin, angiotensinogen, to produce angiotensin I, which is then converted by ACE to AII. The latter substance is a powerful vasopressor agent which has been implicated as a causative agent for producing high blood pressure in various mammalian species, such as the rat, dog, and man. The compounds of this invention inhibit the action of AII at its receptors on target cells and thus prevent the increase in blood pressure produced by this hormone-receptor interaction. By administering a compound of this invention to a species of mammal with hypertension due to AII, the blood pressure is reduced. Administration of a compound of this invention with a diuretic such as furosemide or hydrochlorothiazide, either as a stepwise combined therapy (diuretic first) or as a physical mixture, enhances the antihypertensive effect of the compound. Administration of a compound of this invention with a NSAID can prevent renal failure which sometimes results from administration of a NSAID.

Several peptide analogs of AII are known to inhibit the effects of this hormone by competitively blocking the receptors, but their experimental and clinical applications have been limited by their partial agonist activity and lack of oral absorption (M. Antonaccio, *Clin. Exp. Hypertens.*, **1982**, *A4*, 27-46; D. H. P. Streeten and G. H. Anderson, Jr. - Handbook of Hypertension, Clinical Pharmacology of Antihypertensive Drugs, ed., A. E. Doyle, Vol. 5, pages 246-271, Elsevier Science Publisher, Amsterdam, The Netherlands, 1984).

Several non-peptide antagonists of angiotensin II, including some biphenylmethyl imidazoles, have been disclosed. U.S. Patents 5,137,902 and 5,138,069 disclose biphenylmethylimidazoles (A) where R^1 may be a



(A)

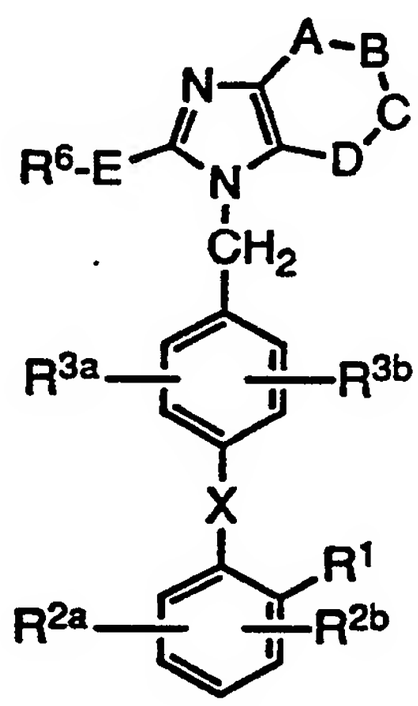


(B)

phenyl substituted in the 2'-position with acidic functional groups, such as carboxy, $-CONHSO_2R$ and tetrazole, and where R^8 may be formyl, acyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkoxyalkyl and hydroxyalkyl. U.S. Applications Serial No. 90/03683 and Serial No. 07/545302 disclose substituted imidazoles of the same basic structure where R^7 may be optionally substituted aryl or heteroaryl. European Application

EP479,479 (Merck) discloses biphenylmethyl imidazoles (B) where R^1B may represent alkyl, R^3 may be H, alkyl, alkenyl or alkynyl, perfluoroalkyl, halogen, NO_2, CN or optionally substituted phenyl, R^4 includes formyl, acyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkoxyalkyl and hydroxyalkyl, X may be a single bond, and R^5 includes $-SO_2NH$-heteroaryl, $-SO_2NHCOR^{12}$ and $-SO_2$ $NHCONR^2R^{12}$, in which R^2 is H or alkyl, and R^{12} is aryl, heteroaryl, cycloalkyl, perfluoroalkyl or optionally substituted C1-C4 alkyl, where the alkyl substituents include aryl, heteroaryl, alkyl, OH, SH, alkoxy, thioalkoxy, halo, carboxy, alkoxycarbonyl, NO_2, optionally substituted amino and various phosphoryl radicals.

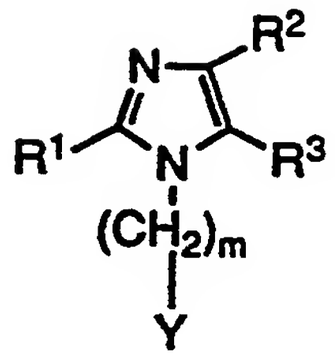
European Application Number 90305850.1 (EP400,974) discloses imidazo-fused 6-membered heterocycles (C) as angiotensin II antagonists useful in the treatment of hypertension and congestive heart failure, where A, B, C,



(C)

and D are independently carbon or nitrogen atoms.

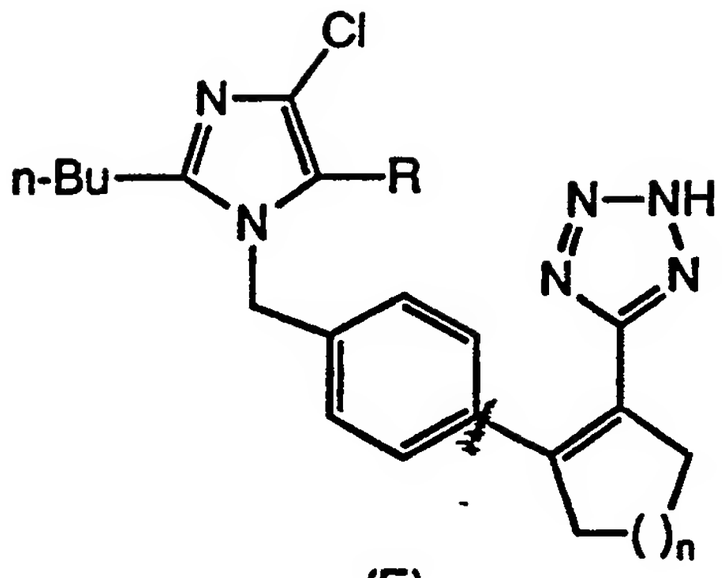
Australian Application AU-A-80163/91 (EP465,368, Roussel-Uclaf) discloses substituted imidazoles (D) where R^1 may be alkyl, m may be 1, either R^2 or R^3 is OR^4, or a sulfurous group of structure $-S(O)_nR^4$,



(D)

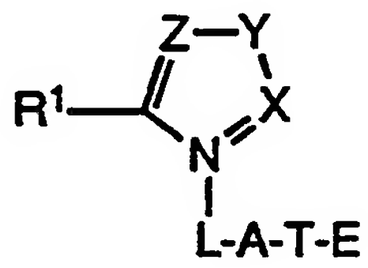
-SO(R4)=NS(O)nX' or -SSR4, where R4 represents a variety of optionally substituted alkyl, alkenyl, alkynyl, acyl or nitrogenous or sulfurous radicals. The imidazole nitrogen substituent $(CH_2)_m$-Y may represent a biphenylmethyl group,which may be substituted in the 2'-position by acidic groups, such as -$(CH_2)_{m1}$-S(O)$_{m2}$-X-R^{10}, in which m1 may be 0-4, m2 may be 0-2, X may be a single bond, -NH-, -NH-CO-, or -NH-CO-NH-and R^{10} is an optionally substituted alkyl, alkenyl, aryl or heteroaryl radical.

H-S. Lin and D. B Boyd, *J. Med. Chem., 1992, 35, 2658-2667,* recently described a series of N-[[4-[2-(2H-Tetrazol-5-yl)-1-cycloalken-1-yl]phenyl]methylimidazole derivatives (E) that are angiotensin II receptor antagonists. The terminal cycloalkenyl ring has a single 5-tetrazoyl substituent. Potency for inhibition of angiotensin II receptors is maximized when the terminal cycloalkenyl is a six-membered ring and an terminal aromatic ring inhibits better than cycloalkenyl.

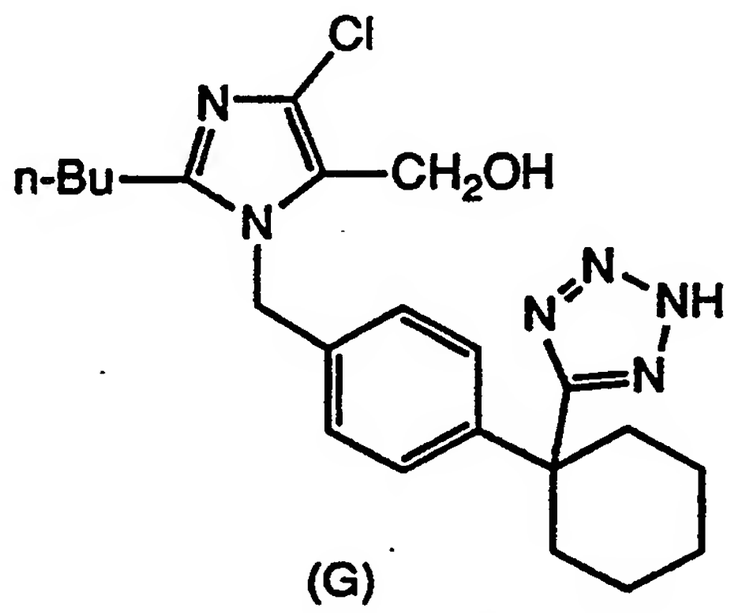


(E)

The European patent application publication no. 485 929 A1 (Hoechst) describes substituted azoles (F) and their use as antagonists of angiotensin II receptors. More specifically the application describes substituted azoles (G).



(F)



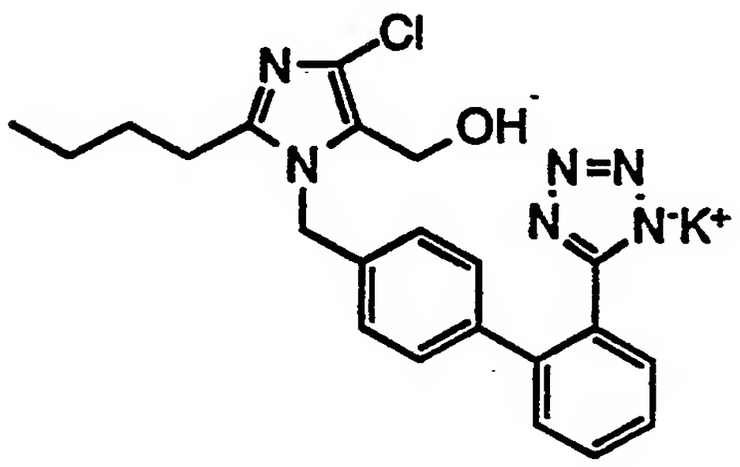
(G)

None of the references describe the compounds of this invention.

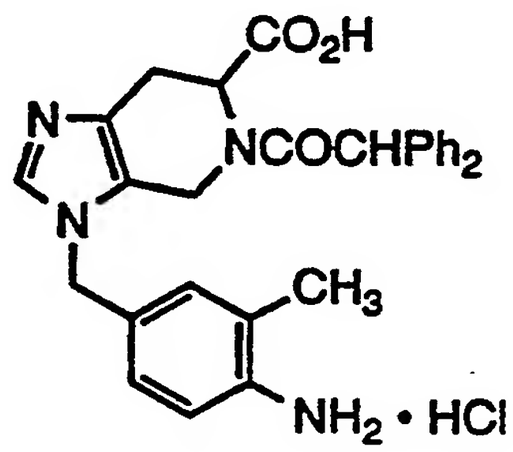
It is well known that two types of angiotensin II receptors are widely distributed in various mammalian tissues (P. C. Wong *et al.*, *Cardiovascular Drug Reviews* **1991**; *9*: 317-339; *Trends in Endocrinol. Metab.* **1992**; *3*: 211-217). The angiotensin II receptor most directly involved in the mediation of blood pressure is termed the AT_1 receptor, and is characterized by high sensitivity to the non-peptide antagonist DuP 753. A second angiotensin II receptor, designated AT_2, is sensitive to another class of non-peptide AII antagonists, represented by PD123177 (ibid.), and

CGP42112A. Angiotensin II has approximately equal affinity for both receptor subtypes.

Recent evidence suggests that the AT_2 receptor may have a role in mediating the synthesis and breakdown of cardiac connective tissues. For example, Matsubara *et*



DuP 753



PD123177

CGP42112A = nicotinic acid-Tyr-(Na-benzyloxy-carbonyl-Arg)Lys-His-Pro-Ile-OH

al. (*The FASEB Journal 6,* 4: A941, **1992**) have reported that PD123177, but not DuP 753, blocks the AII-stimulated inhibition of collagenase in cultured cardiac fibroblasts. Both PD123177 and DuP 753 are reported by Zhou et al. to block the AII-stimulated increase in collagen synthesis in cardiac fibroblasts (*The FASEB Journal 6,* 4: A1914, **1992**).

Tsutsumi and Saavedra have found AT_2 receptors in cerebral arteries (*Am. J. Physiol. 261*: H667-H670, **1991**). An analog of PD123177, PD123319, has been reported by Brix and Haberl (*The FASEB Journal 6,* 4: A1264, **1992**) to block the pial artery dilation induced by angiotensin II in a rat cranial window preparation monitored by intravital microscopy. This suggests that the AT_2 receptor may have a role in modifying cerebral blood flow.

The AT_2 selective antagonist CGP42112A has been reported by LeNoble et al. (*The FASEB Journal 6,* 4:

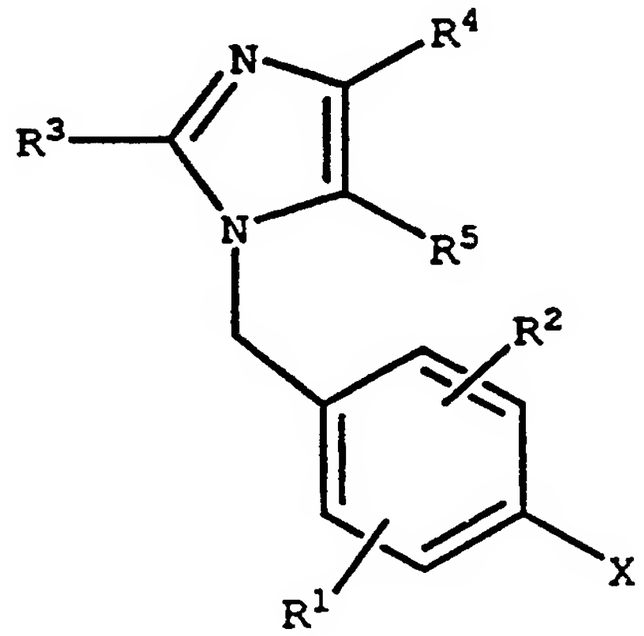
A937, 1992) to block the increase in microvascular density induced by angiotensin II in the chick chorioallantoic membrane, suggesting that angiotensin II may in some contexts mediate angiogenesis through AT_2 receptors.

As noted above, DuP 753, disclosed in U. S. Patent 5,138,069, is a selective AT_1 antagonist, having extremely low affinity for the AT_2 receptor. No data is presented in U. S. Patent 5,138,069 or the other references above which suggests that any of the compounds disclosed possess high AT_2 affinity.

In addition to potent AT_1 antagonist and antihypertensive properties, the imidazole compounds of the present invention possess potent AT_2 antagonist properties. Since AT_1 antagonism leads to increased levels of circulating angiotensin II in vivo (Y. Christen et al., *Am. J. Hypertension,* 1991; 4: 350S-353S), and the AT_2-mediated consequences, if any, of higher AII levels are unknown, simultaneous AT_1/AT_2 antagonism may prove desirable during AT_1-targeted therapy.

SUMMARY OF THE INVENTION

This invention pertains to novel angiotensin-II blocking imidazole compounds of the following Formula (I):



I

wherein

R^1 and R^2 are independently

a) H,

b) C1-C5-alkyl,

c) -OH,

d) C1-C4-alkoxy,

e) $-S(O)_rR^{23}$, or

f) Cl or F;

R^3 is alkyl, alkenyl or alkynyl of 2-7 carbon atoms;

R^4 is

a) H,

b) halogen (Cl, Br, I),

c) C1-C4-alkyl,

d) C1-C4-perfluoroalkyl, or

e) phenyl or phenyl optionally substituted with halogen, C1-C4-alkyl, hydroxyl or C1-C4-alkoxy, or

f) $-S(O)_rR^{23}$;

R^5 is:

a) H,

b) C1-C4 alkyl,

c) $-(CH_2)_mCHR^{15}OR^{16}$,

d) $-COR^{17}$,

e) $-(CH_2)_mCHR^{15}COR^{17}$,

f) $-CR^{18}=CR^{19}COR^{17}$,

g) $-CONHOR^{20}$;

h) $-(CH_2)_mOCOR^{16}$,

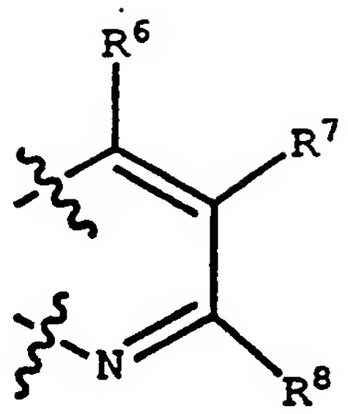
i) $-CH_2NHCOR^{15}$,

j) $-(CH_2)_mNHSO_2R^{23}$,

k) tetrazol-5-yl, or

l) $-CONHSO_2R^9$;

R^4 and R^5 taken together to be



R^6, R^7, R^8 are independently:

a) H,

b) C1-C4-alkyl, either unsubstituted or substituted with:

i) -OH,

ii) $-CO_2R^{16}$,

iii) $-NH_2$,

iv) (C1-C4-alkyl)amino,

v) di(C1-C4-alkyl)amino;

c) halo,

d) $-CF_3$,

e) -OH,

f) $-N(R^{20})_2$,

g) C1-C4-alkoxy,

h) $-CO2R^{16}$,

i) $-CONH_2$,

j) C3-C7-cycloalkyl,

k) aryl, wherein aryl is phenyl or napthyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-$S(O)_r$, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$,

l) heterocyclic, wherein heterocyclic is a five- or six-membered saturated or unsaturated ring containing 1-3 three heteroatoms selected from the group consisting of O, N or S wherein S may be in the form of sulfoxide or sulfone and which may be optionally substituted with one or two substituents

which are members selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-S(O)r, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$,

m) $-CONHSO_2R^9$, or

n) tetrazol-5-yl;

R^9 is:

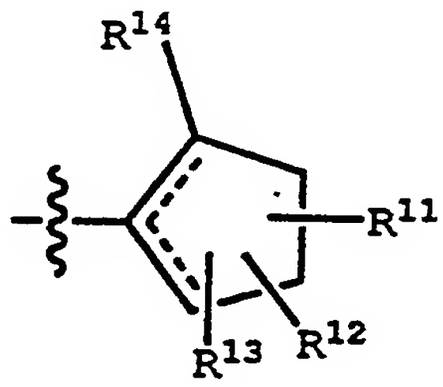
a) C1-C4-alkyl,

b) phenyl or phenyl optionally substituted with halogen, C1-C4-alkyl, -OH or C1-C4-alkoxy;

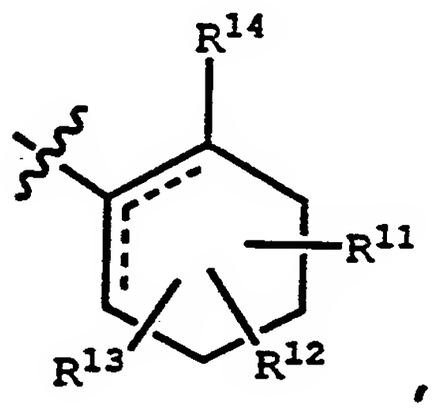
R^{10} is H, C1-C4-alkyl or benzyl;

X is saturated or unsaturated:

a)

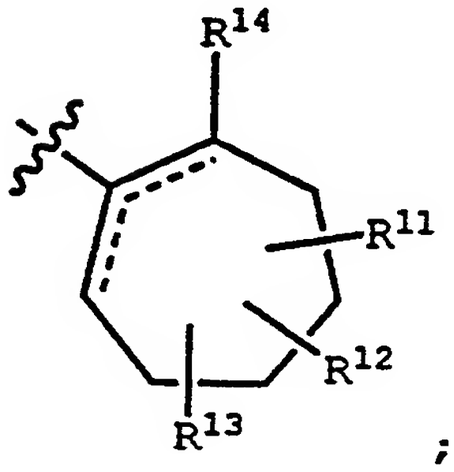


b)



, or

c)



;

R^{11} is

a) C1-C7-alkyl,

b) phenyl or phenyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-S(O), -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$;

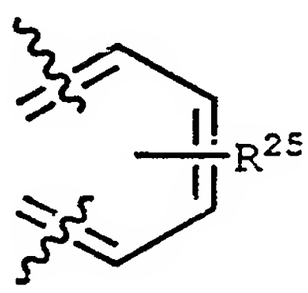
R^{12} and R^{13} are independently

a) H,

b) C2-C7-alkyl,

c) phenyl or phenyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-S(O)-, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, $-CO_2R^{10}$;

R^{12} and R^{13} can be taken together when they are on adjacent carbon atoms to be



R^{14} is:

a) $-CO_2H$,

b) $-SO_2NHCO_2R^{24}$,

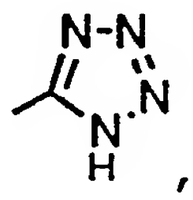
c) $-SO_2NHCOR^{24}$,

d) $-CONHSO_2R^{24}$,

e) $-SO_2NHCONHR^{24}$,

f) $-SO_2NHCSNHR^{24}$, or

g)



,

R^{15} is

a) H,

b) C1-C4-alkyl,

c) C3-C6-cycloalkyl,

d) aryl as defined above, or

e) -(C1-C4-alkyl)aryl,where aryl is as defined above;

R^{16} is

a) H,

b) C1-C6-alkyl,

c) aryl, as defined above,

d) -(C1-C4-alkyl)aryl, where aryl is as defined above, or

e) -(CH2)vCH(aryl)(aryl),where aryl is as defined above;

R^{17} is

a) H,

b) $-OR^{16}$, or

c) $-NR^{21}R^{22}$;

R^{18} and R^{19} are independently

a) H,

b) C1-C4-alkyl,

c) aryl as defined above, or

d) $-CH_2$aryl, where aryl is as defined above;

R^{20} is

a) H,

b) methyl, or

c) benzyl;

R^{21} and R^{22} are independently:

a) H,

b) C1-C4-alkyl,

c) aryl as defined above, or

d) $-CH_2$aryl,where aryl is as defined above,

or taken together comprise

e) $-(CH_2)u-$,where u is 2 to 5, or

f) a morpholine ring;

R^{23} is

a) CF_3,

b) C1-C6-alkyl, or

c) phenyl;

R^{24} is

a) aryl as defined above,

b) C3-C7-cycloalkyl,

c) C1-C4-perfluoroalkyl,

d) C1-C10-alkyl optionally substituted with a substituent selected from the group consisting of:

i) aryl as defined above,

ii) heteroaryl, wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted 5- or 6-membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S and wherein the substituents are members selected from the group consisting of -OH, -SH, C1-C4-alkyl, C1-C4-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2R^{10}$, $-NH_2$, C1-C4-alkylamino, C1-C4-dialkylamino,

iii) -OH, -SH, C1-C4-alkyl, C1-C4-alkoxy, C1-C4-alkylthio, $-CF_3$, halo, $-NO_2$, $-CO_2R^{10}$, $-NH_2$, C1-C4-alkylamino, C1-C4-dialkylamino, $-PO_3H_2$;

e) heteroaryl as defined above;

R^{25} is

a) halo (F, Cl, Br, I),

b) C1-C4-alkyl,

c) C1-C4-alkoxy,

d) $-NO_2$,

e) $-CF_3$,

f) C1-C4-$S(O)_r$

g) -OH,

h) $-NH_2$,

i) -NH(C1-C4-alkyl),

j) $-N(C1-C4-alkyl)_2$,

k) $-CO_2R^{10}$, or

l) H;

m is 0 to 2;

r is 1 to 2;

u is 2 to 5;

v is 0 to 4;

and, the pharmaceutically acceptable salts thereof.

Preferred are compounds of Formula I wherein:

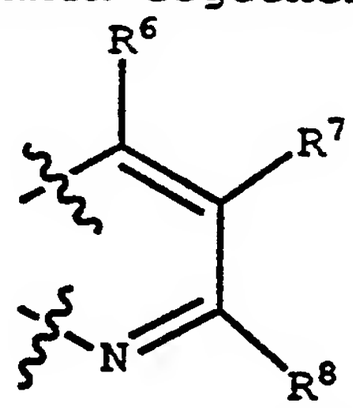
a) $-(CH_2)_mCHR^{15}OR^{16}$,

b) $-COR^{17}$,

c) $-(CH_2)_mCHR^{15}COR^{17}$, or

d) $-CONHSO_2R^9$;

R^4 and R^5 taken together to be



R^6, R^7, R^8 are independently:

a) H,

b) C1-C4-alkyl,

c) halo,

d) $-CF_3$

e) $-N(R^{20})2$,

h) $-CO_2R^{16}$

i) $-CONHSO_2R^9$, or

j) tetrazol-5-yl;

R^{24} is

a) aryl as defined above,

b) C3-C7-cycloalkyl,

c) C1-C4-perfluoroalkyl,

d) C1-C10-alkyl optionally subsituted with phenyl.

and, the pharmaceutically acceptable salts thereof.

Specifically preferred compounds include:

- 1-[[4-(2-carboxy-4-phenylcyclohexen-1-yl)phenyl]methyl]-4-chloro-5-hydroxymethyl-2-propylimidazole

- 1-[[4-[2-carboxy-4-(1,1-dimethylethyl)cyclohexen-1-yl]phenyl]methyl]-4-chloro-5-hydroxymethyl-2-propylimidazole

- 5,7-dimethy-2-ethyl-3-[[4-[2-carboxy-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-4,4-diphenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-4-propylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-3-phenylcyclohexen-1 -yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 1-[[4-[2-carboxy-4-(1,1-dimethylethyl)cyclohexen-1 -yl]phenyl]methyl]-4-ethyl-2-propylimidazole-5-carboxaldehyde

- 5,7-dimethy-2-ethyl-3-[[4-[2-(1 H-tetrazol-5-yl)-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 1-[[4-[2-(1H-tetrazol-5-yl)-4-(1,1-dimethylethyl)cyclohexen-1-yl]phenyl]methyl]-4-ethyl-2-propylimidazole-5-carboxaldehyde

- 5,7-dimethy-2-ethyl-3-[[4-[2-[[(butoxycarbonyl)amino]sulfonyl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

It should be noted in the foregoing structural formula, when a radical can be a substituent in more than one previously defined radical, that first radical can be selected independently in each previously defined radical. For example, $R^1$and R^2 can each be $-SO_2R^{25}$. R^{25} need not be the same substituent in each of R^1 and R^2, but can be selected independently for each of them.

It is understood that many of the compounds of the present invention contain one or more chiral centers and that these stereoisomers may possess distinct physical and biological properties. The present invention comprises all of the stereoisomers or mixtures thereof. If the pure enantiomers or diastereomers are desired, they may be prepared using starting materials with the appropriate stereochemistry, or may be separated from mixtures of undesired stereoisomers by standard techniques, including chiral chromatography and recrystallization of diastereomeric salts.

Note that throughout the text when an alkyl substituent is mentioned, the normal alkyl structure is meant (e.g. butyl is n-butyl) unless otherwise specified. However, in the definition of radicals above (e.g. R^3), both branched and straight chains are included in the scope of alkyl, alkenyl and alkynyl.

Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a non-exhaustive list of which is given in Remington's Pharmaceutical Sciences 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts.

Also within the scope of this invention are pharmaceutical compositions comprising a suitable pharmaceutical carrier and a novel compound of Formula (I), and methods of using the novel compounds of Formula (I) to treat hypertension and congestive heart failure. The pharmaceutical compositions can optionally contain one or more other therapeutic agents, such as a diuretic, an angiotensin I converting enzyme (ACE) inhibitor or a non-steroidal antiinflammatory drug (NSAID). Also within the scope of this invention is a method of preventing renal failure resulting from administration of a NSAID which comprises administering a novel compound of Formula (I) in stepwise or physical combination with the NSAID. The compounds of this invention can also be used as diagnostic agents to test the renin angiotensin system.

DETAILED DESCRIPTION OF THE INVENTION

SYNTHESIS

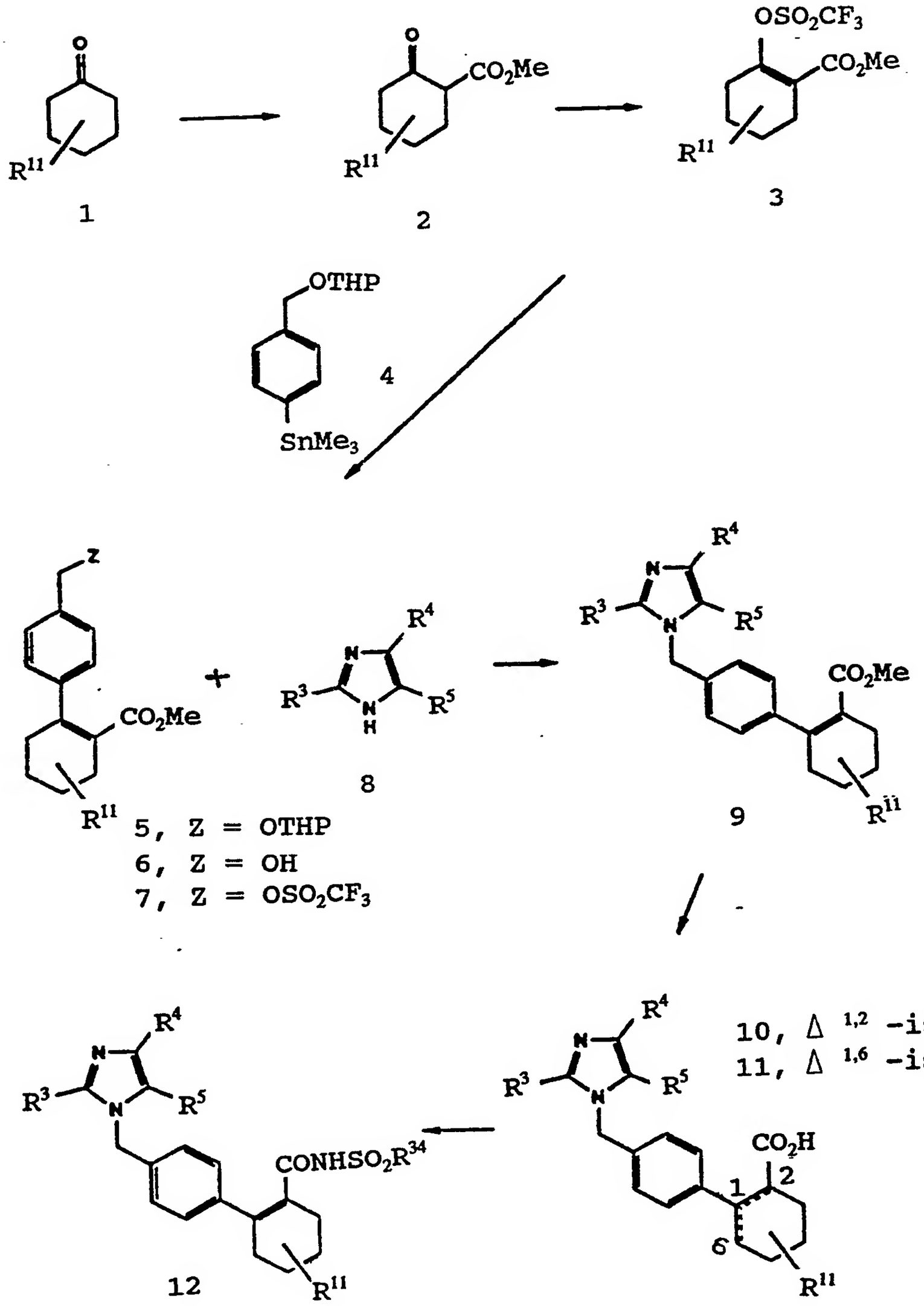
The novel compounds of Formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is

understood by those skilled in the art of organic synthesis that the functionality present on the molecule must be consistent with the chemical transformations proposed. Throughout the following section, not all compounds of Formula (I) falling into a given class may necessarily be prepared by all methods described for that class. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described. This will frequently necessitate judgment as to the order of synthetic steps, protecting groups required, and the choice of alternate methods for effecting various transformations. Such restrictions to the substituents will be readily apparent to one skilled in the art.

The carboxylic acids (I, $R^{14} = CO_2H$) and sulfonylamides (I, $R^{14} = CONHSO_2R^{24}$) of this invention generally can be prepared as shown in Scheme 1. However, for simplicity, the chemistry of Scheme 1 is demonstrated employing the monosubstituted cyclohexanone **1** (R^{12},R^{13} = H) as starting material. The requisite cycloalkanones are available commercially or are readily prepared by procedures available in the literature.

The treatment of cyclohexanone **1** with a non-nucleophilic base such as lithium diisopropylamide intetrahydrofuran at $^{-}$78 - 0°C followed by treatment with methyl chloroformate or methyl cyanoformate provided the 2-(carbomethoxy)cyclohexanone **2**. This compound was converted to the triflate **3** by treatment with trifluoromethane sulfonic anhydride in the presence of a base such as triethylamine in an inert solvent such as methylene chloride at $^{-}$78 - 25°C. Alternatively, **2** can be deprotonated with sodium hydride in ether at 0°C

SCHEME 1


R11
1
CO2Me
2
OSO2CF3
CO2Me
3
OTHP
4
SnMe3
Z
CO2Me
R11
5, Z = OTHP
6, Z = OH
7, Z = OSO2CF3
R4
N
R3
N
H
R5
8
R4
N
R3
N
R5
CO2Me
9
R11
R4
N
R3
N
R5
10, Δ 1,2 -isomer
11, Δ 1,6 -isomer
CO2H
1
2
6
R11
CONHSO2R34
12
R11

and then allowed to react with trifluoromethanesulfonic anhydride. Stannane **4** is then coupled to triflate **3** employing a palladium catalyst (J.K. Stille and W.J. Scott *J. Am. Chem. Soc.*, **1986**,*108*, 3033; A.M. Echavarren and J.K. Stille *J. Am. Chem. Soc.*,**1987**,*109*, 5478; I.N. Houpis, *Tetrahedron Lett.*, **1991**, *32*, 6675). For example, compounds **3** and **4** together with a catalytic quantity of tetrakis(triphenylphosphine)palladium(0) and lithium chloride are mixed and refluxed in an inert solvent such as dioxane to yield **5**. However, this coupling reaction can be performed faster and in better yield employing bis(benzonitrile)palladium dichloride and tris(2-furyl)phosphine as the catalyst system. Deprotection of **5** in methanol containing a catalytic amount of toluenesulfonic acid provided the alcohol **6**, and **6** was then converted to the corresponding mesylate **7** by treatment with methanesulfonyl chloride and triethylamine in methylene chloride.

Alkylation of an imidazole derivative **8** with the mesylate **7** in a solvent such as dimethylforamide, tetrahydrofuran, or dimethylsulfoxide in the presence of an acid scavenger such as sodium or potassium carbonate, sodium or potassium bicarbonate, Huenig's base, or collidine at room temperature to the reflux temperature of the solvent affords **9**. Alternatively, the imidazole **8** can be deprotonated with a base followed by alkylation with **7** in the solvents and at the temperatures described above. Effective bases include sodium or potassium hydride, lithium diisopropylamide, sodium methoxide, and potassium t-butoxide. The mesylate **7** can also be replaced in these alkylations by the corresponding tosylate or bromide which can be prepared from **6** by procedures well known to one skilled in the art.

The ester **9** is saponified to the carboxylic acid **10** by stirring in tetrahydrofuran or methanol in the presence of 1 to 20 equivalents of aqueous 1-10 N sodium or potassium hydroxide at room temperature to the reflux temperature of the solvent. Depending upon substitution patterns, intermediates such as **9** are subject to

migration of the double bond when treated with base. Therefore, the saponification generally provides varying amounts of the $D^{1,6}$ -isomer **11** in addition to the $D^{1,2}$ -isomer **10**.

The cycloalkene system may be hydrogenated to yield the fully saturated system in inert solvents such as tetrahydrofuran or methanol using catalysts such as 5-10% palladium/carbon or platinum oxide, a procedure familiar to one skilled in the art. The double bond may also be reduced by dissolving metal-type reductions employing magnesium (T. Hudlicky, G. Sinai-Zingde, M.G. Natchus, *Tetrahedron Lett.*, **1987**, *28*, 5287), stannous chloride (H. Rakoff, B.H. Miles, *J. Org. Chem.*, **1961**, *26*, 2581), zinc/acetic acid (D.J. Goldsmith, C. Kwong, G. Srousi, *J. Org. Chem.*, **1978**, *43*, 3182), or homogeneous reducing agents such as RED-Al/cuprous bromide (M.F. Semmelhack, R.D. Stauffer, *J. Org. Chem.*, **1975**, *40*, 3619).

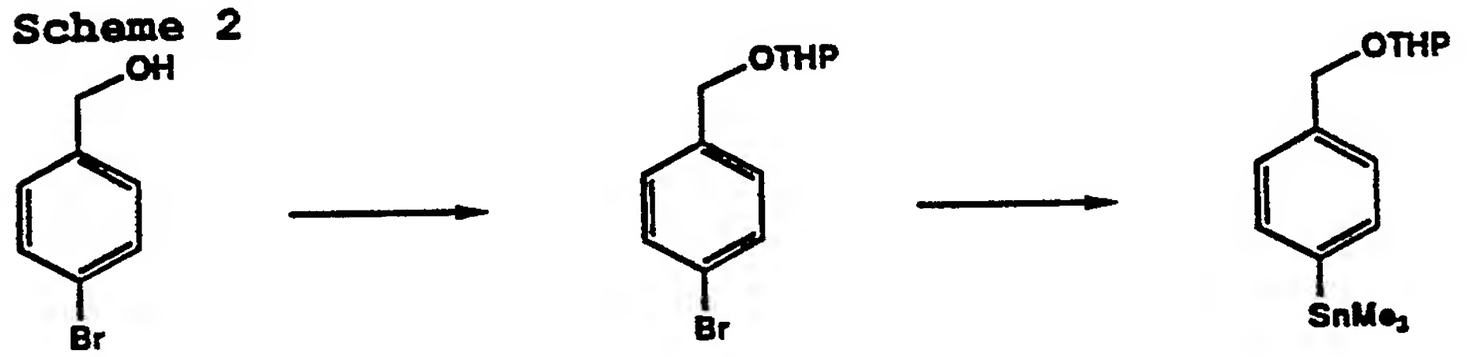
The carboxylic acid **10** may be allowed to react with carbonyl diimidazole in an inert solvent at 25°C to the reflux temperature of the solvent followed by treatment with a sulfonamide in the presence of a non-nucleophilic base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) at 25°C to the reflux temperature of the solvent to provide the sulfonylamide **12**.

The imidazole derivatives **8** may be synthesized as described in U.S. Patent No. 5,137,902 and 5,138,069 as well as Australian Pat. Appl. AU-A-80163/91,while the imidazopyridines (**8**, R^4,R^5 is $-C(R^6)=C(R^7)-C(R^8)=N-$) can be synthesized by the procedures disclosed in Eur. Pat. Appl. 400974 (1990).

The preparation of stannane **4** is shown in Scheme 2. Benzyl alcohol **13** is first protected with a THP group in an inert solvent such as ether or tetrahydrofuran using dihydropyran and a catalytic amount of an acid such as toluenesulfonic acid or phosphorus oxychloride to furnish **14**. The alcohol **13** may also be protected with a variety of other protecting groups compatible with the subsequent chemistry. These groups include MEM, MOM,

TBDMS, and methyl ether (see T. W. Greene "Protective Groups in Organic Chemistry", Wiley-Interscience: New York, 1981; pp. 10-50) and which are familiar to one skilled in the art. The bromide **14** then can be reacted with magnesium to form the Grignard reagent, or **14** can be treated with n- or sec-butyllithium to provide the corresponding aryllithium reagent by halogen-lithium exchange. The organometallic reagent (RMgBr or RLi) is then allowed to react with trimethylstannyl chloride in an inert solvent such as ether, tetrahydrofuran, or dioxane at 0-25°C to provide **4**. Alternatively, the stannanes (e.g.4) can be prepared by treatment of the corresponding iodides with hexamethylditin in the presence of a palladium catalyst such as tetrakis-(triphenylphosphine)palladium (W.D. Wulff, et al., *J. Org. Chem.*, **1986**, 51, 277).

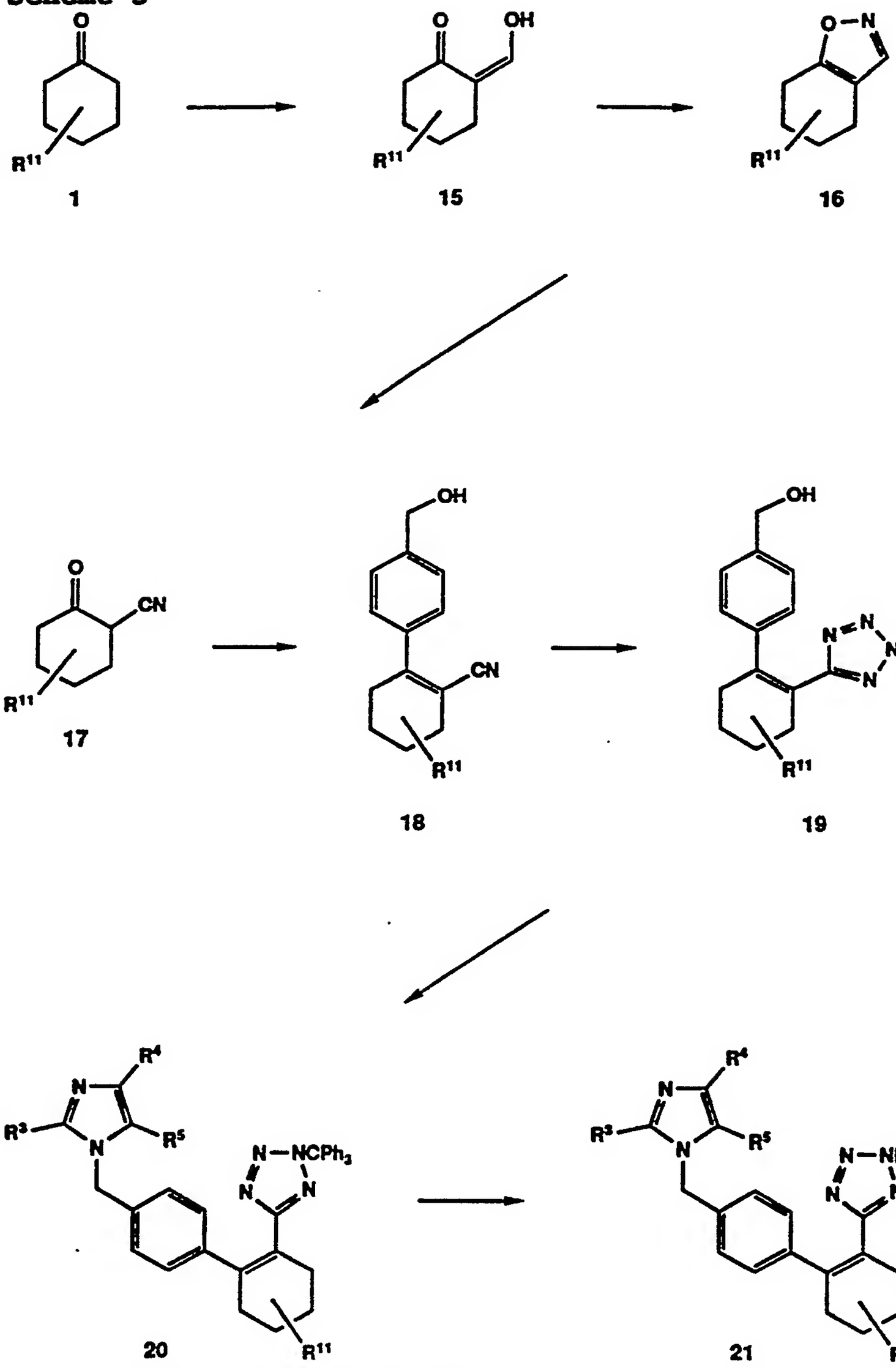
Scheme 2



13 **14** **4**

The tetrazoles of this invention (I, R^{14} = CN_4H) can be prepared as shown in Scheme 3. A three step procedure was employed for the preparation of the requisite α°C cyanocyclohexanone **17** (W. L. Meyers, R. W. Huffman, and P. G. Schroeder, *Tetrahedron*, **1968**, *24*, 5959). In this procedure the cyclohexanone **1** was formylated with ethyl formate in the presence of a base such as sodium methoxide in an inert solvent such as benzene or toluene at 0-25°C to provide **15**. Treatment of **15** with hydroxylamine in a solvent such as acetic acid at 25°C to the reflux temperature of the solvent afforded the

Scheme 3



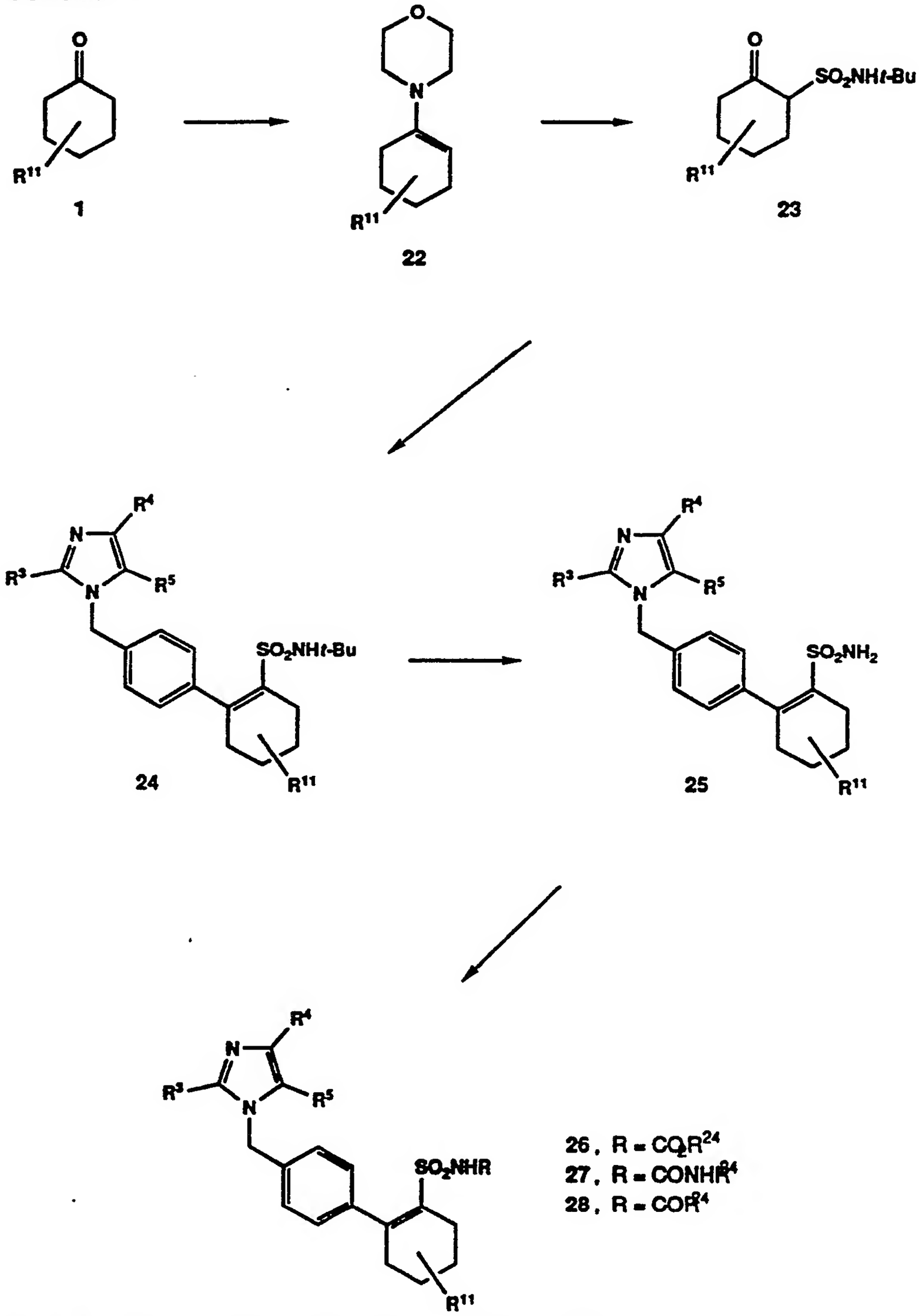
isoxazole **16**, which upon exposure to base in a system such as sodium ethoxide in refluxing ethanol furnished **17**. Alternatively, **17** can be prepared by quenching the

enolate of **1** with a source of electrophilic cyanide such as tosylcyanide (D. Kahne, D. B. Collum, *Tetrahedron Lett.*, **1981**, *22*, 5011).

The α-cyanocyclohexanone **17** was converted into **18** employing the same procedures described in Scheme 1 for the transformation of **2** into **6**. Treatment of **18** with a trialkyltin azide reagent, followed by removal of the trialkylstannyl residue and protection of the free tetrazole with the triphenylmethyl group, afforded **19** (D. J. Carini, J. V. Duncia, U. S. Patent No. 5138069). Employing the mesylation and alkylation procedures described in Scheme 1, the alcohol **19** was converted into **20**. Finally, deprotection of **20** by exposure to an aqueous acid such as hydrochloric acid in an organic solvent such as tetrahydrofuran afforded **21**. Alternatively, the deprotection can be performed by refluxing **20** in a solvent such as methanol.

The acylsulfonamides (**I**, R^{14} = SO_2NHCOR^{24}, $SO_2NHCO_2R^{24}$, or $SO_2NHCONHR^{24}$) of this invention may be prepared as shown in Scheme 4. The cyclohexanone **1** is readily converted by procedures know to one skilled in the art into a variety of cyclic enamines, for example the morpholine enamine **22**. Treatment of **22** with an aminosulfonylchloride, $RNHSO_2Cl$, in the presence of a base such as triethylamine and in an inert solvent such as methylene chloride affords, following a hydrolytic work-up, a ß-ketosulfonamide (A. Bender, D. Guenther, L. Willms, R. Wingen, *Synthesis*, **1985**, 66). For example the *t*-butylsulfonamide **23** is employed in this scheme. At this point **23** can be readily converted to **24** by a series of procedures analogous to those described in Scheme 1. Stirring a solution of **24** in trifluoroacetic acid or trifluoroacetic acid/methylene chloride at a temperature from 25°C to the reflux temperature of the solvent provides the primary sulfonamide **25**. Finally, treatment

Scheme 4



of **25** with a chloroformate, $ClCO_2R^{24}$, in the presence of a base such as pyridine and in an inert solvent such as

methylene chloride provides the carbamate **26**. Alternatively, the primary sulfonamide **25** can be treated with an isocyanate, $R^{24}NCO$, to afford the urea **27** or with an activated carboxylic acid derivative to furnish the amide **28**. The active carboxylic acid derivatives employed for the preparation of the amides may include acid chlorides ($R^{24}COCl$), acid anhydrides [$(R^{24}CO)_2O$], or carboxylic acids ($R^{24}CO_2H$) which have been activated by treatment with carbonyldiimidazole or dicyclohexylcarbodiimide.

Example 1

Part A: Preparation of 2-carbomethoxy-4-phenylcyclohexanone

To a solution of diisopropylamine (12.6 mL, 90 mmol, 1.2 eq) in tetrahydrofuran (240 mL) at -25 °C was added dropwise 2.1 M n-butyllithium in hexane (43.7 mL, 90 mmol, 1.2 eq), and the resulting solution was stirred at -25 °C for 0.5 h. The solution was cooled to -78 °C, and 4-phenylcyclohexanone (13.1 g, 75 mmol, 1.0 eq) was added. The reaction mixture was allowed to warm to 0 °C and then was stirred at 0 °C for 1.0 h. The mixture again was cooled to -78 °C. To this solution was added dropwise hexamethylphosphoric triamide (13 mL, 75 mmol, 1.0 eq) followed by methyl cyanoformate (7.2 mL, 90 mmol, 1.2 eq). After stirring at -78 °C for 0.2 h the reaction mixture was poured into ice-cold water, and the resulting mixture was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 1-chlorobutane) followed by recrystallization from 1-chloro-butane/hexane to afford 9.18 g of 2-carbomethoxy-4-phenylcyclohexane: mp 59-63 °C; NMR (300

MHz, $CDCl_3$) δ 12.20 (s, 1 H), 7.38-7.18 (m, 5 H), 3.77 (s, 3 H), 2.80-2.23 (m, 5 H), 2.00 (m, 1 H), 1.85 (m, 1 H).

Part B: Preparation of 2-carbomethoxy-4-phenyl-1-(trifluoromethane-sulfonyloxy)cyclohexene

To a suspension of hexane-washed sodium hydride (1.41 g, 58.5 mmol, 1.5 eq) in diethyl ether (300 mL) at 25 °C was added 2-carbomethoxy-4-phenylcyclohexane (9.10 g, 39 mmol, 1.0 eq). After the foaming ceased the resulting mixture was cooled to 0 °C. To this mixture was added dropwise trifluoromethanesulfonic anhydride (6.60 mL, 39 mmol, 1.0 eq). The reaction mixture was stirred at 0 °C for 3 h and then was allowed to warm to 25 °C. The mixture was diluted with water and then extracted with diethyl ether. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 1-chlorobutane) followed by recrystallization from hexane furnished 9.67 g of 2-carbomethoxy-4-phenyl-1-(trifluoromethane sulfonyloxy)cyclohexene: mp 43.5-45 °C; NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5 H), 3.81 (s, 3 H), 2.94-2.80 (m, 2 H), 2.70-2.45 (m, 3 H), 2.10 (m, 1 H), 1.97 (m, 1 H).

Part C: Preparation of 1-bromo-4-[(tetrahydropyran-2-yloxy)methyl]benzene

A mixture of 4-bromobenzyl alcohol (50.00 g, 270 mmol, 1 eq), 3,4-dihydro-2H-pyran (26.98 mL, 300 mmol, 1.1 eq), phosphorous oxychloride (0.3 mL), and ethyl ether (300 mL) was stirred for 48 h at 25 °C. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution, water, and brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product

was chromatographed on silica gel (elution: 95:5 hexanes/ethyl acetate) to provide 18.92 g of 1-bromo-4-[(tetrahydropyran-2-yloxy)methyl]benzene as a colorless oil. NMR (300 MHz, $CDCl_3$) δ 7.46 (d, 2 H, J = 9 Hz); 7.24 (d, 2 H, J = 9 Hz); 4.73 (d, 1 H, J = 12 Hz); 4.68 (m, 1 H); 4.44 (d, 1 H, J = 12 Hz); 3.88 (m, 1 H); 3.54 (m, 1 H); 1.92-1.48 (m, 6 H).

Part D: Preparation of 1-[(tetrahydropyran-2-yloxy)methyl]-4-(trimethylstannyl)benzene.

A solution of 1-bromo-4-[(tetrahydropyran-2-yloxy)methyl]benzene (5.00g, 18.5 mmol, 1 eq) in tetrahydrofuran (75 mL) at 25 °C was added to a suspension of freshly ground magnesium turnings (0.90 g, 36.9 mmol, 2 eq) in tetrahydrofuran (75 mL) at 25 °C. After initiation of the reaction cooling was applied as necessary to maintain the reaction temperature under 35 °C. After the exothermic reaction ceased the solution was stirred at 25 °C for 1 h, was cooled to 0 °C, and then was added to a solution of trimethyltin chloride (4.40g, 22.1 mmol, 1.2 eq) in tetrahydrofuran (50 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 16 h and then was poured into a 5% aqueous ammonium chloride solution. The phases were separated, and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 1-chlorobutane) afforded 4.4 g of 1-[(tetrahydropyran-2-yloxy)methyl]-4-(trimethylstannyl)benzene as an oil. NMR (300 MHz,$CDCl_3$) δ 7.48 (d, 2 H, J = 9 Hz); 7.35 (d, 2 H, J = 9 Hz); 4.77 (d, 1 H, J = 12 Hz); 4.72 (t, 1 H, J = 2 Hz); 4.48 (d, 1 H, J = 12 Hz); 3.92 (m, 1 H); 3.54 (m, 1 H); 1.94-1.47 (m, 6 H); 0.27 (t, 9 H, J =.24 Hz).

Part E: Preparation of 4-(2-carbomethoxy-4-phenylcyclohexen-1-yl)-1-[(tetrahydropyran-2-yloxy)methyl]benzene

To a mixture of 2-carbomethoxy-4-phenyl-1-(trifluoromethane-sulfonyloxy)cyclohexene (11.0 g, 30 mmol, 1.0 eq), 1-[(tetrahydropyran-2-yloxy)methyl]-4-(trimethylstannyl)benzene (11.8 g, 33 mmol, 1.1 eq), and lithium chloride (3.77 g, 90 mmol, 3.0 eq) in dioxane (250 mL) at 25 °C was added tris(2-furyl)phosphine (0.69 g, 3.0 mmol, 0.1 eq) followed by bis(benzonitrile)palladium(II) chloride (0.58 g, 1.5 mmol, 0.05 eq), and the resulting reaction mixture was refluxed for 2 h. After cooling the mixture was diluted with water and extracted with 1-chlorobutane. The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-10% ethyl acetate/benzene) provided 12.4 g of 4-(2-carbomethoxy-4-phenyl-cyclohexen-1-yl)-1-[(tetrahydropyran-2-yloxy)methyl]benzene as a colorless oil.

Part F: Preparation of 4-(2-carbomethoxy-4-phenylcyclohexen-1-yl)benzyl alcohol

A solution of 4-(2-carbomethoxy-4-phenylcyclohexen-1-yl)-1-[(tetrahydropyran-2-yloxy)methyl]benzene (11.1 g, 27 mmol, 1.0 eq) and p-toluenesulfonic acid monohydrate (0.53 g, 2.8 mmol, 0.1 eq) in methanol (250 mL) was stirred at 25 °C for 2.5 h. The methanol was removed under vacuum, and the residue was dissolved in ethyl acetate. The resulting organic solution was washed with saturated aqueous sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-10% ethyl acetate/methylene chloride)

followed by recrystallization from toluene/hexane provided 6.54 g of 4-(2-carbomethoxy-4-phenylcyclohexen-1-yl)benzyl alcohol: mp 78-78.5 °C; NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (m, 9 H), 4.69 (d, 2 H, J = 5.5 Hz), 3.46 (s, 3 H), 2.99-2.79 (m, 2 H), 2.60-2.42 (m, 3 H), 2.13-1.76 (m, 3 H).

Part G: Preparation of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4.5-b]pyridine

To a solution of 5,7-dimethyl-2-ethylimidazo[4,5-b]pyridine (0.58 g, 3.3 mmol, 1.00 eq) in dimethylformamide (12 mL) at 25 °C was added 60% sodium hydride in oil (0.132 9, 5.5 mmol, 1.67 eq). When the foaming had subsided the mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. To the reaction mixture was added a solution of mesylate (prepared from 4-[2-[N(triphenylmethyl)tetrazol-S-yl]-4-phenylcyclohexen- 1 -yl] benzyl alcohol (1.90 9, 3.3 mmol, 1.00 eq) by the procedure described in Example 1, Part G) in dimethylformamide (12 mL). The resulting solution was stirred at 25 °C for 20 h. The solvent was removed under vacuum, and the residue was dissolved in methylene chloride. The solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-10% ethyl acetate/benzene) afforded 1.91 g of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl) tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4, 5-b] pyridine; NMR (300 MHz, CDC13) d 7.36-7.16 (m, 14 H), 6.96 (d, 2 H, J = 8 Hz), 6.906.85 (m, 9 H), 5.33 (s, 2 H), 3.03 (m, 2 H), 2.69-2.53 (m, 11 H), 2.151.91 (m, 2 H), 1.22 (t, 3 H, J = 7 Hz).

Part H: Preparation of 5,7-dimethyl-2-ethyl-3-[[4-[2-(1 H-tetrazol-5yl)-4-phenylcyclohexen-1-yl]phenyl]methyl]= 3H-imidazo[4, 5-bl pyridine

A solution of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine (1.90 9, 2.6 mmol), tetrahydrofuran (200 mL), and 10% hydrochloric acid (100 mL) was stirred at 25 °C for 16 h. The solution was poured into excess aqueous sodium hydroxide, and the resulting mixture was reduced to ~10% of its original volume under vacuum and then filtered. The heterogeneous solids were not washed with water but were suspended in 300-400 mL of water. The mixture was stirred at room temperature until the white, powdery solid had dissolved to leave a suspension of a waxy, colorless solid. This suspension was filtered, and the filtrate was acidified to pH 3.5 employing hydrochloric acid. The resulting precipitate was recovered by filtration, washed with water, and dried. Recrystallization of the crude product from ethyl acetate provided 0.81g of 5,7-dimethyl-2-ethyl-3-[[4-[2-(1H-tetrazol-5-yl)-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4, 5-b] pyridine: mp 204-206 °C; NMR (300 MHz, DMSO-d_6)δ 7.35 (m, 4 H), 7.24 (m, 1 H), 6.98 (s, 4 H), 6.95 (s, 1 H), 5.40 (s, 2 H), 3.09-2.50 (m, 7 H), 2.49 (s, 6 H), 1.99 (m, 2 H), 1.19 (t, 3 H, J = 7 Hz).

Part I: Preparation of 1-[[4-(2-carboxy-4-phenylcyclohexen-1-yl)phenyl]methyl]-4-chloro-5-(hydroxymethyl)-2-propylimidazole

To a solution of 1-[[4-(2-carbomethoxy-4-phenylcyclohexen-1-yl)phenyl]methyl]-4-chloro-5-(hydroxymethyl)-2-propylimidazole (1.66 g, 3.5 mmol) in methanol (70 mL) at 25 °C was added 10% aqueous sodium

hydroxide (35 mL), and the mixture was refluxed for 1 h. After cooling the solvent was removed under vacuum, and the residue was dissolved in water. The solution was acidifed to pH 3 employing hydrochloric acid, and the precipitate was filtered, dried, and recrystallized from acetone to provide 1.02 g of 1-[[4-(2-carboxy-4-phenylcyclohexen-1-yl)phenyl]-methyl]-4-chloro-5-(hydroxymethyl)-2-propylimidazole: mp 207-209.5 °C; NMR (300 MHz, DMSO-d_6) δ 7.31 (m, 4 H), 7.23-7.16 (m, 3 H), 7.02 (d, 2 H, J = 8 Hz), 5.24 (m, 3 H), 4.31 (s, 2 H), 2.88 (m, 1 H), 2.62 (br d, 1 H, J = 17 Hz), 2.54-2.33 (m, 5 H), 1.90 (m, 2 H), 1.51 (sext, 2 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz).

Example 2

Part A: Preparation of 2-hydroxymethylene-4-phenylcyclohexanone

To a mixture of ethyl formate (70 mL, 865 mmol, 3.0 eq) and sodium methoxide (17.2 g, 320 mmol, 1.1 eq) in benzene (150 mL) at 5 °C was added dropwise a solution of 4-phenylcyclohexanone (50.3 g, 290 mmol, 1.0 eq) in benzene (150 mL). The mixture was stirred at 5 °C for 2.5 h during which time a heavy precipitate formed. The reaction mixture was diluted with water, acidified to pH 3-4 with hydrochloric acid, and then extracted with benzene. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was recrystallized from 1-chlorobutane to provide 25.5 g of 2-hydroxymethylene-4-phenyl-cyclohexanone: mp 81.5-83 °C; NMR (300 MHz, $CDCl_3$) δ 14.45 (br s, 1 H), 8.70 (m, 1 H), 7.37-7.22 (m, 5 H), 2.84 (m, 1 H), 2.68-2.44 (m, 4 H), 2.05 (m, 1 H), 1.88 (m, 1H).

Part B: Preparation of 4, 5, 6, 7-tetrahydro-5-phenyl-1, 2-benzisoxazole

A solution of 2-hydroxymethylene-4-phenylcyclohexanone (25.35 g, 125 mmol, 1.0 eq), hydroxylamine hydrochloride (12.65 g, 182 mmol, 1.5 eq), and acetic acid (200 mL) was refluxed for 0.5 h. After the mixture had cooled the solvent was removed under vacuum. The residue was dissolved in water and extracted with toluene. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: toluene) afforded 17.2 g of product as a 6:1 mixture of 4, 5, 6, 7-tetrahydro-5-phenyl-1, 2-benzisoxazole and its regioisomer; NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 0.15 H), 8.08 (s, 0.85 H), 7.37-7.24 (m, 5 H), 3.10-2.73 (m, 4 H), 2.66-2.54 (m, 1 H), 2.20 (m, 1 H), 2.12-1.93 (m, 1 H).

Part C: Preparation of 2-cyano-4-phenylcyclohexanone

To ethanol (300 mL) at 25 °C was added sodium metal (2.00 g, 87 mmol, 1.0 eq) in portions. When the sodium had dissolved 4, 5, 6, 7-tetrahydro-5-phenyl-1, 2-benzisoxazole (14.5 g, 73 mmol, 1.2 eq) was added. The resulting solution was reflux for 1 h, during which time a white precipitate formed. After cooling the solvent was removed under vacuum. The residue was dissolved in water, and the resulting aqueous suspension was filtered. The filtrate was acidified to pH 2.5 employing hydrochloric acid and extracted with methylene chloride. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to furnish 11.0 g of 2-cyano-4-phenylcyclohexanone, which was employed in the subsequent reaction without further purification.

Part D: Preparation of 2-cyano-4-phenyl-1-(trifluoromethanesulfonyloxy)-cyclohexene

To a solution of 2-cyano-4-phenylcyclohexanone (8.36 g, 42 mmol, 1.00 eq) and triethylamine (6.27 mL, 45 mmol, 1.07 eq) in methylene chloride (200 mL) at -78 °C was added dropwise trifluoromethanesulfonic anhydride (7.11 mL, 42 mmol, 1.00 eq), and the resulting mixture was stirred at -78 °C for 2 h. The mixture was poured into water, and the resulting emulsion was extracted with methylene chloride. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: benzene) provided 13.5 g of 2-cyano-4-phenyl-1-(trifluoromethanesulfonyloxy)cyclohexene; NMR (300 MHz, $CDCl_3$) δ 7.38-7.19 (m, 5 H), 2.94 (m, 1 H), 2.68 (m, 4 H), 2.16 (m, 1 H), 2.02 (m, 1 H).

Part E: Preparation of 4-(2-cyano-4-phenylcyclohexen-1-yl)benzyl alcohol

This compound was prepared from 2-cyano-4-phenyl-1-(trifluoromethanesulfonyloxy)cyclohexene and 1-[(tetrahydropyran-2-yloxy)methyl]-4-(trimethylstannyl)benzene (from Example 1, Part D) employing the procedures described in Example 1, Parts E and F; mp: 103-104.5 °C; NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1 H), 7.36 (m, 2 H), 7.27 (m, 3 H), 4.72 (d, 2 H, J = 6 Hz), 2.96 (m, 1 H), 2.76-2.52 (m, 4 H), 2.14 (m, 1 H), 1.95 (m, 1 H), 1.81 (t, 1 H, J = 6 Hz).

Part F: Preparation of 4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]benzyl alcohol

A solution of 4-(2-cyano-4-phenylcyclohexen-1-yl)benzyl alcohol (5.79 g, 20 mmol, 1.00 eq), trimethyltin azide (5.15 g, 25 mmol, 1.25 eq), and

xylenes (80 mL) was stirred at 120 °C for 72 h. Additional trimethyltin azide (1.29 g, 6.2 mmol, 0.30 eq) was added at 24 h into the reaction, and again an identical portion was added at 48 h. During the course of the reaction a heavy white precipitate formed. After allowing the reaction mixture to cool to ~80 °C it was filtered. The solids were washed with warm xylenes and dried. These solids were suspended in a mixture of methylene chloride (72 mL) and tetrahydrofuran (14 mL) at 25 °C. To this suspension was added dropwise 10 N sodium hydroxide (2.00 mL, 20 mmol, 1.00 eq) and the mixture was stirred at 25 °C for 0.2 h. To this mixture was added triphenylmethyl chloride (5.46 g, 20 mmol, 1.00 eq), and the resulting reaction mixture was stirred at 25 °C for 3.5 h. The mixture was diluted with methylene chloride, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-10% ethyl acetate/hexane) followed by recrystallization from benzene/hexane furnished 7.79 g of 4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]benzyl alcohol: mp 166-167 °C; NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 14 H), 7.09 (A_2B_2, 4 H, J = 8 Hz), 6.84 (d, 6 H, J = 8 Hz), 4.53 (d, 2 H, J = 6 Hz), 3.08 (m, 2 H), 2.66 (m, 3 H), 2.18-1.94 (m, 2 H), 1.44 (t, 1 H, J = 6 Hz).

Part G: Preparation of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

To a solution of 5,7-dimethyl-2-ethylimidazo[4,5-b]pyridine (0.58 g, 3.3 mmol, 1.00 eq) in dimethylformamide (12 mL) at 25 °C was added 60% sodium hydride in oil (0.132 g, 5.5 mmol, 1.67 eq). When the foaming had subsided the mixture was stirred at 50 °C for 1 h and then cooled to 0 °C. To the reaction mixture

was added a solution of mesylate (prepared from 4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]benzyl alcohol (1.90 g, 3.3 mmol, 1.00 eq) by the procedure described in Example 1, Part G) in dimethylformamide (12 mL). The resulting solution was stirred at 25 °C for 20 h. The solvent was removed under vacuum, and the residue was dissolved in methylene chloride. The solution was washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-10% ethyl acetate/benzene) afforded 1.91 g of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine; NMR (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 14 H), 6.96 (d, 2 H, J = 8 Hz), 6.90-6.85 (m, 9 H), 5.33 (s, 2 H), 3.03 (m, 2 H), 2.69-2.53 (m, 11 H), 2.15-1.91 (m, 2 H), 1.22 (t, 3 H, J = 7 Hz).

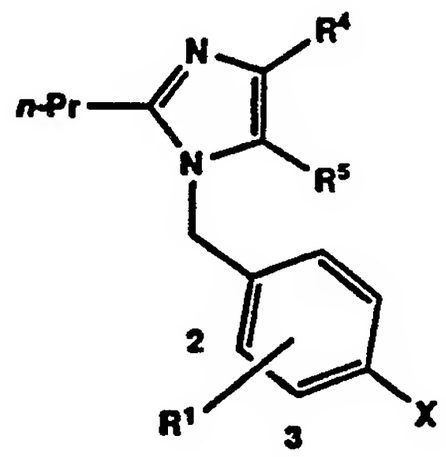
Part H: Preparation of 5,7-dimethyl-2-ethyl-3-[[4-[2-(1H-tetrazol-5-yl)-4-phenylcyclohexen-1-yl]phenyl]methyl]]-3H-imidazo[4,5-b]pyridine

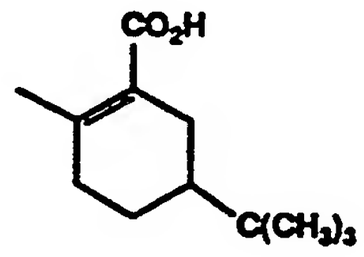
A solution of 5,7-dimethyl-2-ethyl-3-[[4-[2-[N-(triphenylmethyl)tetrazol-5-yl]-4-phenylcyclohexen-1-yl]phenyl]methyl]]-3H-imidazo[4,5-b]pyridine (1.90 g, 2.6 mmol), tetrahydrofuran (200 mL), and 10% hydrochloric acid (100 mL) was stirred at 25 °C for 16 h. The solution was poured into excess aqueous sodium hydroxide, and the resulting mixture was reduced to ~10% of its original volume under vacuum and then filtered. The heterogeneous solids were not washed with water but were suspended in 300-400 mL of water. The mixture was stirred at room temperature until the white, powdery solid had dissolved to leave a suspension of a waxy, colorless solid. This suspension was filtered, and the filtrate was acidified to pH 3.5 employing hydrochloric

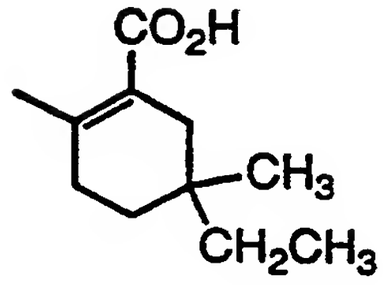
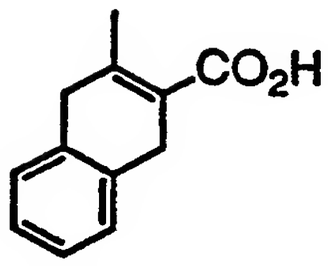
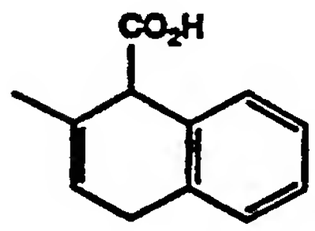
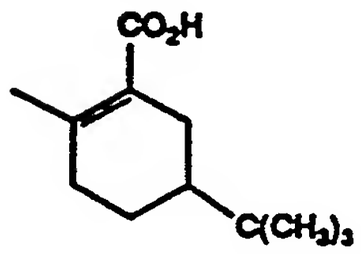
acid. The resulting precipitate was recovered by filtration, washed with water, and dried. Recrystallization of the crude product from ethyl acetate provided 0.81 g of 5,7-dimethyl-2-ethyl-3-[[4-[2-(1H-tetrazol-5-yl)-4-phenylcyclohexen-1-yl]-phenyl]methyl]-3H-imidazo[4,5-b]pyridine: mp 204-206 °C; NMR (300 MHz, DMSO-d_6) δ 7.35 (m, 4 H), 7.24 (m, 1 H), 6.98 (s, 4 H), 6.95 (s, 1 H), 5.40 (s, 2 H), 3.09-2.50 (m, 7 H), 2.49 (s, 6 H), 1.99 (m, 2 H), 1.19 (t, 3 H, J = 7 Hz).

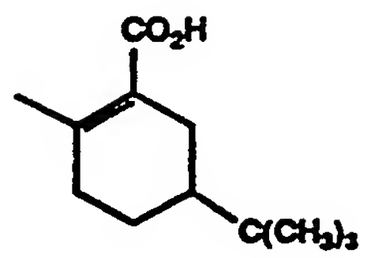
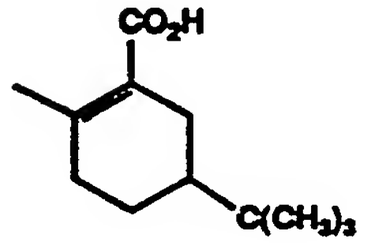
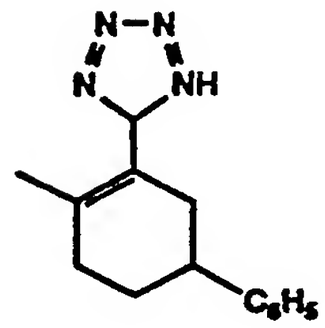
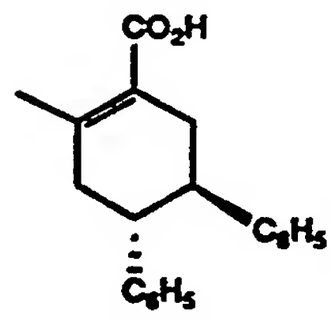
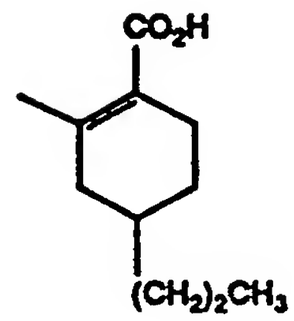
The compounds in Tables 1 and 2 were or could be synthesized employing the procedures described above for the preparation of Examples 1 and 2, by chemistry otherwise described in this case, or by methods familiar to one skilled in the art.

Table 1



Ex.	R^4	R^5	R^1	X	mp
3	Cl	CH_2OH	H		155-158°C
4	-	-	-	(-)-enantiomer	144-145°C

5	5	"	"	(+)-enantiomer	144-145°C
	6	Cl	CH_2OH	H	
	7	Cl	CH_2OH	H	
	8	Cl	CH_2OH	H	 204-206°C
	9	Et	CO_2H	H	 182-183°C

10	Et	CHO	H			200-201°C
11	Cl	CO_2H	H			205-205.5°C
12	Et	CHO	H			a
13	Et	CHO	H			
14	Et	$COCH_3$	H			

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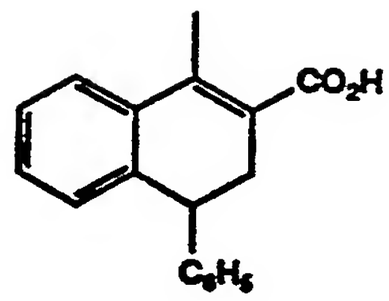
15	Cl	CH_2OH	H	

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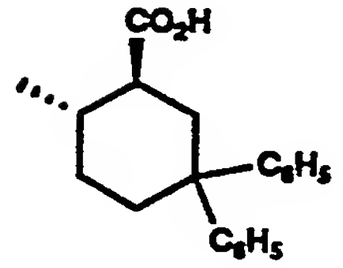
16	Et	CO_2H	H	

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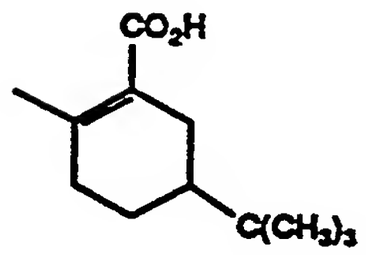
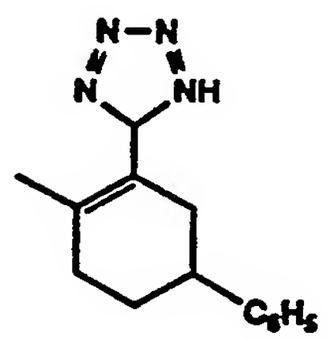
17	Et	CO_2CH_3	2-OCH_3	

18	Et	CHO	2-CH_3	

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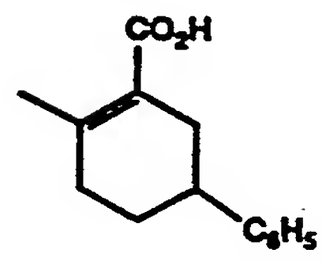
19	Et	CHO	3-SCH_3	

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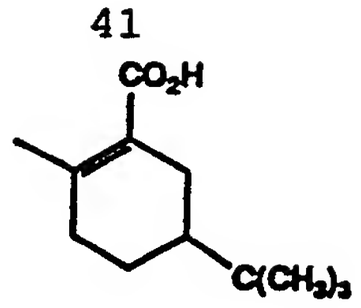
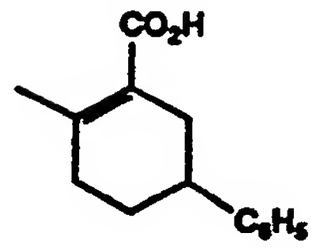
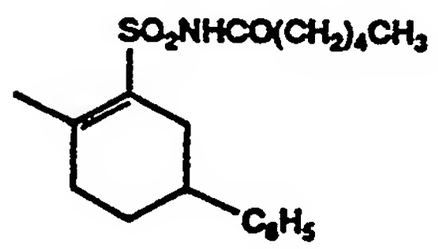
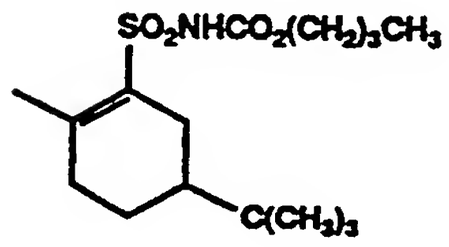
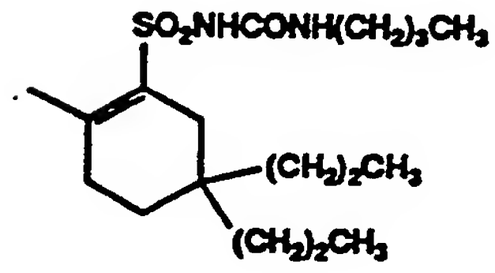
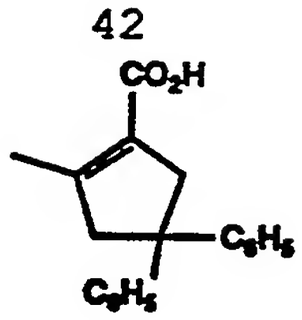
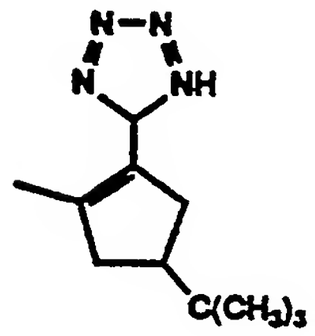
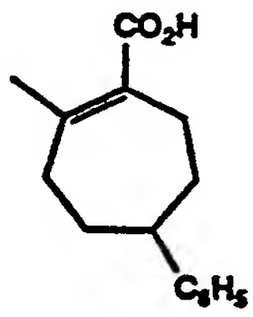
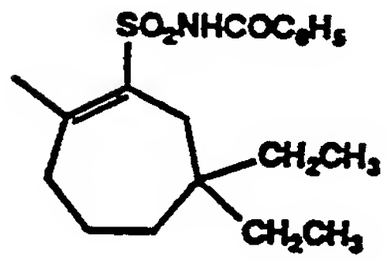
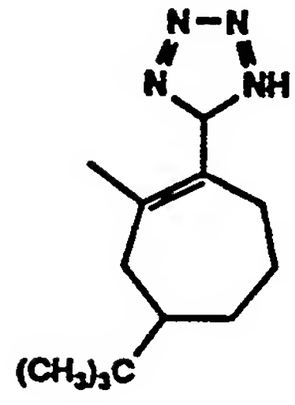
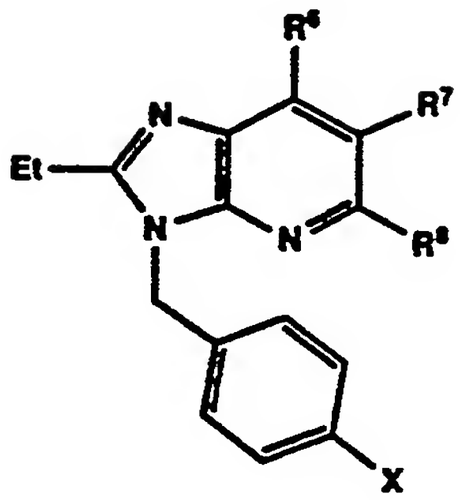
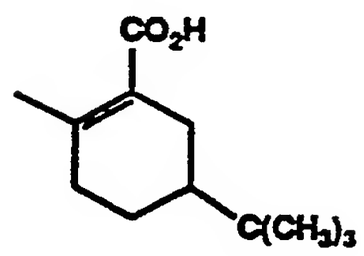
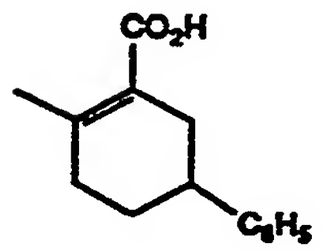
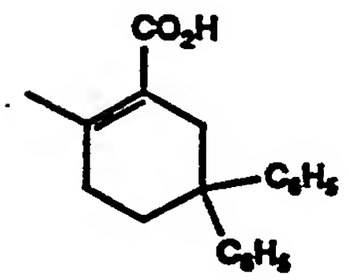
20	Ph	CO_2CH_3	H	
21	Ph	CHO	H	
22	CF_2CF_3	CO_2H	H	
23	Ph	CHO	H	
24	Et	CO_2H	H	

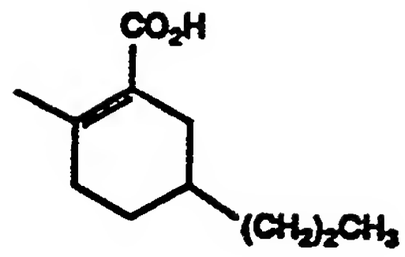
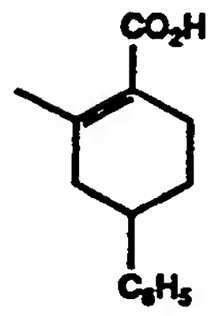
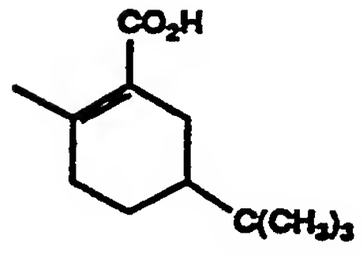
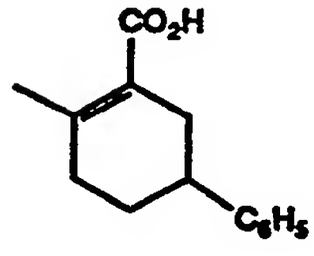
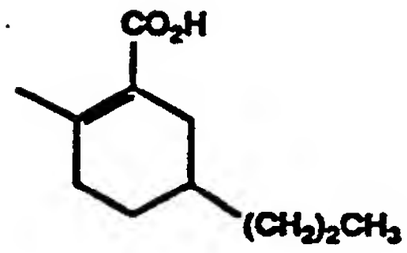
25	Cl	CH_2OH	H		42
26	Et	$COCH_3$	H		
27	Ph	CHO	H		
28	Cl	CO_2CH_3	H		
29	Et	CO_2H	H		

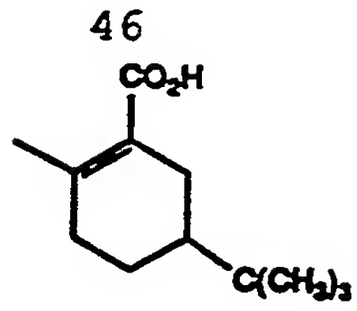
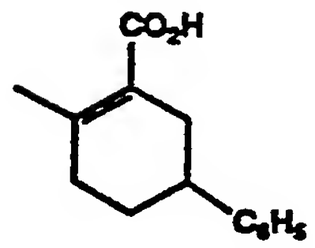
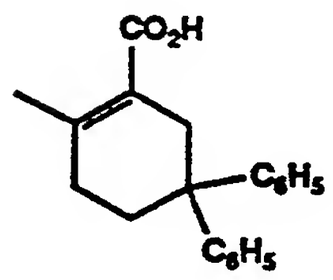
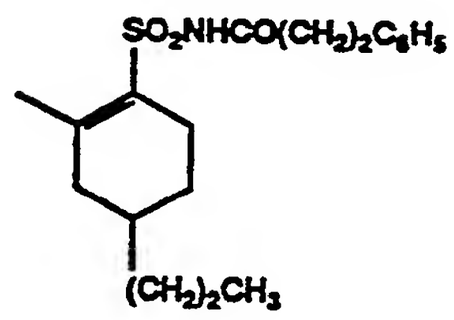
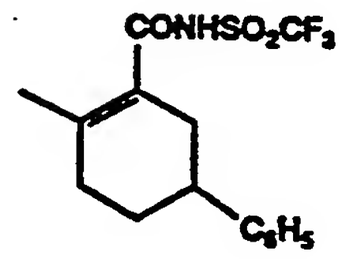
a NMR (300 MHz, DMSO-d_6) δ 9.74 (s, 1 H), 7.34-7.31 (m, 4 H), 7.24 (m, 1 H), 6.99 (d, 2 H, J = 8 Hz), 6.91 (d, 2 H, J = 8 Hz), 5.51 (s, 2 H), 3.05 (m, 1 H), 2.84-2.72 (m, 3 H), 2.60-2.50 (m, 5 H), 2.00 (m, 2 H), 1.54 (sext, 2 H, J = 7 Hz), 1.21 (t, 3 H, J = 7 Hz), 0.83 (t, 3 H, J = 7 Hz).

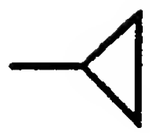
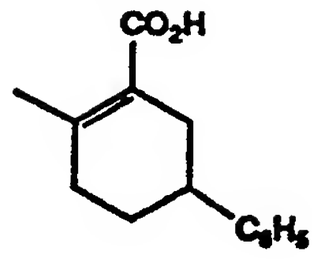
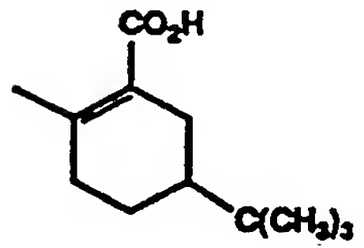
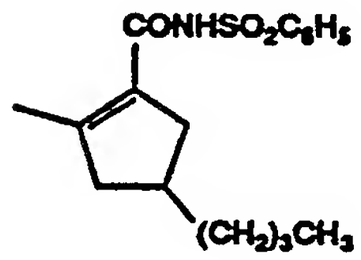
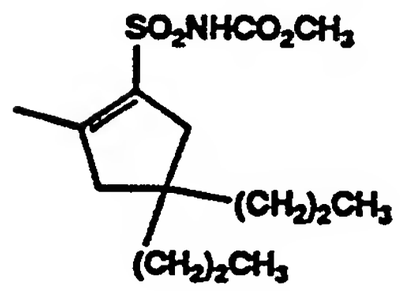
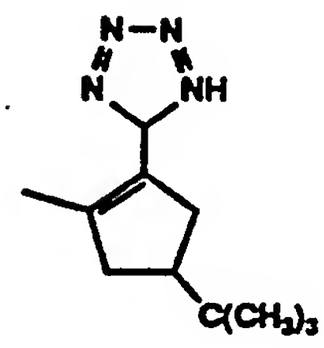
Table 2

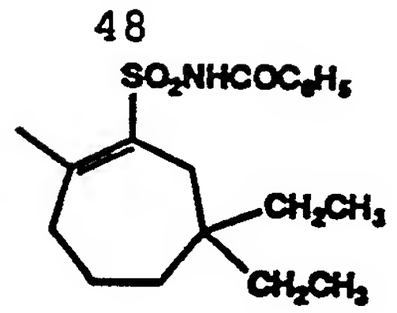
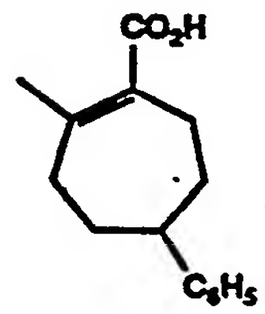
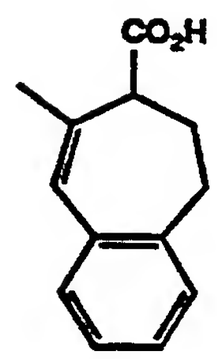


Ex.	R^6	R^7	R^8	X	mp
30	CH_3	H	CH_3		229-230°C
31	CH_3	H	CH_3		210.5-214.5°C
32	CH_3	H	CH_3		242-246°C

33	CH_3	H	CH_3			186-187°C
34	CH_3	H	CH_3			248-251°C
35	CH_3	H	CO_2H			
36	H	Ph	H			
37	H	OEt	H			

38	CH_3	$CONH_2$	CH_3	
39	*n*-Bu	H	CH_3	
40	H	CF_3	H	
41	CH_3	H	CH_3	
42	CH_3	H	CH_3	

43	H		H	
44	Et	H	Et	
45	CH_3	H	CH_3	
46	CH_3	H	CH_3	
47	CH_3	H	CH_3	

48	CH_3	H	CH_3		
49	CH_3	H	CH_3		
50	CH_3	H	CH_3		

Utility

Angiotensin-II (AII) produces numerous biological responses (e.g. vasoconstriction) through stimulation of its receptors on cell membranes. For the purpose of identifying compounds such as AII antagonists which are capable of interacting with AII receptors, a ligand-receptor binding assay was utilized.

DuP 753 and PD123177 were used as standards, and to block angiotensin II binding to the AT_1 and AT_2 sites, respectively. DuP 753 was synthesized according to the procedures described by Carini and Duncia (U. S. 5,138,069). PD123177 was prepared using the methods described by Blankely et al. (U. S. 4,812,462).

AT_1 site binding was determined in a rat adrenal cortical microsome preparation or in a rat liver

membrane preparation. Results for AT_1 binding were similar in both assays. AT_2 site binding was determined using a rat adrenal medulla preparation. For the adrenal cortical microsome and adrenal medulla preparations, the method of Chiu, et al. (*Receptor, 1,* 33, **1990**) was employed. For the liver membrane preparation, the method of Bauer et al. (*Molecular Pharmacology, 39,* 579-585, **1991**) was used, with the following changes: male Charles River CD rats were employed; the homogenation buffer consisted of a solution of Trizma base (10 mM) and EDTA (5.0 mM) adjusted to pH 7.5 with 1N HCl; the binding buffer consisted of a solution of Trizma base (50 mM) and $MgCl_2$ $6H_2O$ (5 mM) adjusted to pH 7.20 with 6N HCl; and the binding was assessed using a 96 well plate format at 22°C. To illustrate the adrenal cortex assay, in brief, aliquots of a freshly prepared particulate fraction of rat adrenal cortex were incubated with 0.15 nM [^{125}I] AII and varying concentrations of potential AII antagonists in a Tris buffer. After a 1 h incubation the reaction was terminated by addition of cold assay buffer. The bound and free radioactivity were rapidly separated through glass-fiber filters, and the trapped radioactivity was quantitated by gamma counting. The inhibitory concentration (IC_{50}) of potential AII antagonists which gives 50% displacement of the total specifically bound [^{125}I] AII is presented as a measure of the affinity of such compound for the AII receptor. AT_1 site binding was determined in the presence of 10^{-6} M PD123177. AT_2 site binding was determined in the presence of 10^{-6} M DuP 753. IC_{50} was determined by displacement of [^{125}I] AII from the receptor by the test compound.

Using the assay method described above, the compounds of this invention are found to exhibit an

activity of at least IC_{50} <10 micromolar at both the AT_1 and AT_2 receptors, thereby demonstrating and confirming the activity of these compounds as effective AT_1/AT_2 AII receptor antagonists.

The potential antihypertensive effects of the compounds of this invention may be demonstrated by administering the compounds to awake rats made hypertensive by ligation of the left renal artery (Cangiano, et al., *J. Pharmacol. Exp. Ther.*, *208*, 310, 1979). This procedure increases blood pressure by increasing renin production with consequent elevation of AII levels. Compounds are administered intravenously via cannula in the jugular vein to give a cumulative dose of 10 mg/kg. Arterial blood pressure is continuously measured directly through a carotid artery cannula and recorded using a pressure transducer and a polygraph. Blood pressure levels after treatment are compared to pretreatment levels to determine the antihypertensive effects of the compounds.

Using the in vivo methodology described above, the compounds of this invention are found to exhibit an activity (intravenous) which is 10 mg/kg or less, and/or an activity (oral) which is 100 mg/kg or less, thereby demonstrating and confirming the utility of these compounds as effective agents in lowering blood pressure.

The compounds of this invention are useful in treating hypertension, and for the treatment of hyperuricemia, primary and secondary hyperaldosteronism, psoriasis, cardiac disorders such as acute and chronic congestive heart failure, angina pectoris, myocardial infarction, systolic and diastolic dysfunction, cardiac myopathy, and cardiac hypertrophy and hyperplasia, esp. left ventricular hypertrophy; pulmonary disorders such as primary and secondary pulmonary hypertension; vascular disorders such as atherosclerosis, restenosis

after vascular injury associated with e.g. angioplasty or bypass surgery, vascular hypertrophy and hyperplasia, atheroma and Raynaud's disease; cerebrovascular disorders such as migraine, and ischemic and hemorragic stroke; renal disorders such as renal vascular hypertension, proteinuria of primary renal disease, end stage renal disease and renal transplant therapy, glomerulonephritis, nephrotic syndrome, scleroderma and glomerular sclerosis, and for enhancing renal blood flow; CNS disorders such as impairment of cognitive function and memory loss, addiction, anxiety, bulimia, depression, epilepsy, pain, Parkinson's disease, psychosis, sleep disorders and tardive dyskinesia; ocular disorders such as macular degeneration and elevated intraocular pressure; gastrointestinal and bladder disorders; disorders associated with diabetes, such as diabetic angiopathy, nephropathy and retinopathy, and for delaying the onset of type II diabetes. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art. The compounds of this invention are also useful as diagnostic agents, to test the renin angiotensin system.

Patients in need of treatment for elevated intraocular pressure can be treated with compounds of this invention administered in the form of typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically contain about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention. For this use, the compounds of this invention may also be used in combination with other medications for the treatment of glaucoma including choline esterase inhibitors such as

physostigmine salicylate or demecarium bromide, parasympathomimetic agents such as pilocarpine nitrate, beta-adrenergic antagonists such as timolol maleate, adrenergic agonists such as epinephrine and carbonic anhydrase inhibitors such as MK-507.

In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized with a pharmaceutical carrier in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 1 to 1000 mg per patient per day which can be administered in single or multiple doses. Preferably, the dosage range will be about 5 to 500 mg per patient per day; more preferably about 5 to 300 mg per patient per day.

Administration of a compound of this invention with a NSAID can prevent renal failure which sometimes results from administration of a NSAID. The compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics. Administration of a compound of this invention with a diuretic, either as a stepwise combined therapy (diuretic first) or as a physical mixture, enhances the antihypertensive effect of the compound. For example, the compounds of this invention can be given in combination with diuretics such as

hydrochlorothiazide, chlorothiazide, chlorthalidone, methylclothiazide, furosemide, ethacrynic acid, triamterene, amiloride spironolactone and atriopeptin; calcium channel blockers, such as diltiazem, felodipine, nifedipine, amlodipine, nimodipine, isradipine, nitrendipine and verapamil; ß-adrenergic antagonists such as timolol, atenolol, metoprolol, propanolol, nadolol and pindolol; angiotensin converting enzyme inhibitors such as enalapril, lisinopril, captopril, ramipril, quinapril and zofenopril; renin inhibitors such as A-69729, FK 906 and FK 744; α-adrenergic antagonists such as prazosin, doxazosin, and terazosin; sympatholytic agents such as methyldopa, clonidine and guanabenz; atriopeptidase inhibitors (alone or with ANP) such as UK-79300; serotonin antagonists such as ketanserin; A_2-adrenosine receptor agonists such as CGS 22492C; potassium channel agonists such as pinacidil and cromakalim; and various other antihypertensive drugs including reserpine, minoxidil, guanethidine, hydralazine hydrochloride and sodium nitroprusside as well as combinations of the above-named drugs. Combinations useful in the management of congestive heart failure include, in addition, compounds of this invention with cardiac stimulants such as dobutamine and xamoterol and phosphodiesterase inhibitors including amrinone and milrinone.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly. To illustrate these combinations, one of the angiotensin-II antagonists of this invention effective clinically in the 5-500 milligrams per day range can be effectively combined at levels at the 1.0-500 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (6-

100 mg), chlorothiazide (125-500 mg), ethacrynic acid (5-200 mg), amiloride (5-20 mg), furosemide (5-80 mg), propranolol (10-480 mg), timolol maleate (1-20 mg), methyldopa (125-2000 mg), felodipine (1-20 mg), nifedipine (5-120 mg), nitrendipine (5-60 mg), and diltiazem (30-540 mg). In addition, triple drug combinations of hydrochlorothiazide (5-100 mg) plus amiloride (5-20 mg) plus angiotensin-II antagonists of this invention (1-500 mg) or hydrochlorothiazide (5-100 mg) plus timolol maleate (5-60 mg) plus an angiotensin-II antagonists of this invention (1-500 mg) or hydrochlorothiazide (5-200 mg) and nifedipine (5-60 mg) plus an angiotensin-II antagonist of this invention (1-500 mg) are effective combinations to control blood pressure in hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin

capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

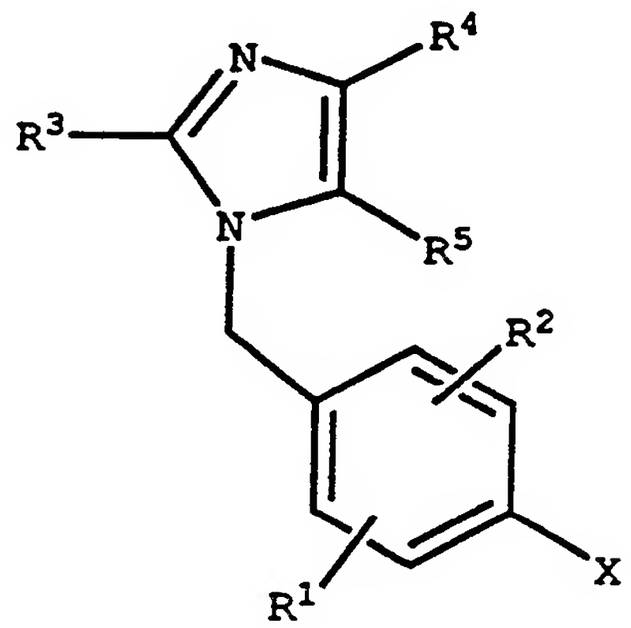
Suspension

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise in conjunction with another therapeutic agent. When the drugs are administered in physical combination, the dosage form and administration route should be selected for compatibility with both drugs.

CLAIMS

1. A compound of Formula I



I

wherein

R^1 and R^2 are independently

a) H,

b) C1-C5-alkyl,

c) -OH,

d) C1-C4-alkoxy,

e) $-S(O)_rR^{23}$, or

f) Cl or F;

R^3 is alkyl, alkenyl or alkynyl of 2-7 carbon atoms;

R^4 is

a) H,

b) halogen (Cl, Br, I),

c) C1-C4-alkyl,

d) C1-C4-perfluoroalkyl, or

e) phenyl or phenyl optionally substituted with halogen, C1-C4-alkyl, hydroxyl or C1-C4-alkoxy, or

f) $-S(O)_rR^{23}$;

R^5 is:

a) H,

b) C1-C4 alkyl,

c) $-(CH_2)_mCHR^{15}OR^{16}$,

d) $-COR^{17}$,

e) $-(CH_2)_mCHR^{15}COR^{17}$,

f) $-CR^{18}=CR^{19}COR^{17}$,

g) $-CONHOR^{20}$;

h) $-(CH_2)_mOCOR^{16}$,

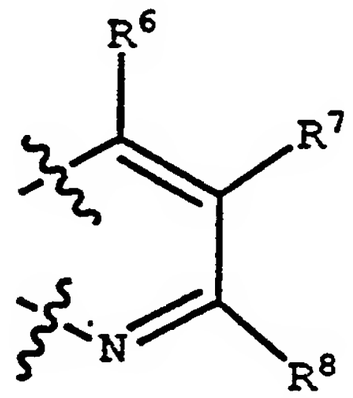
i) $-CH_2NHCOR^{15}$,

j) $-(CH_2)_mNHSO_2R^{23}$,

k) tetrazol-5-yl, or

l) $-CONHSO_2R^9$;

or R^4 and R^5 taken together may be



R^6, R^7, R^8 are independently:

a) H,

b) C1-C4-alkyl, either unsubstituted or substituted with:

i) -OH,

ii) $-CO_2R^{16}$,

iii) $-NH_2$,

iv) (C1-C4-alkyl)amino,

v) di(C1-C4-alkyl)amino;

c) halo,

d) $-CF_3$,

e) -OH,

f) $-N(R^{20})_2$,

g) C1-C4-alkoxy,

h) $-CO_2R^{16}$,

i) $-CONH_2$,

j) C3-C7-cycloalkyl,

k) aryl, wherein aryl is phenyl or napthyl optionally substituted with one or two substituents

selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-$S(O)_r$, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$,

l) heterocyclic, wherein heterocyclic is a five- or six-membered saturated or unsaturated ring containing 1-3 three heteroatoms selected from the group consisting of O, N or S wherein S may be in the form of sulfoxide or sulfone and which may be optionally substituted with one or two substituents which are members selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-$S(O)_r$, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$,

m) $-CONHSO_2R^9$, or

n) tetrazol-5-yl;

R^9 is:

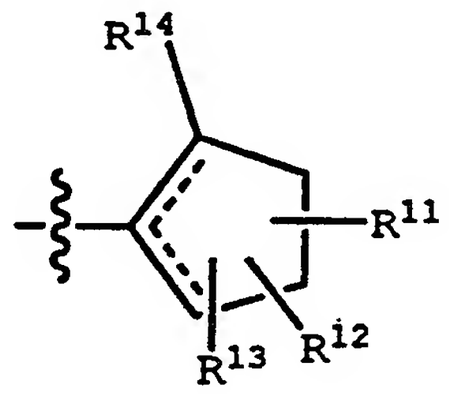
a) C1-C4-alkyl,

b) phenyl or phenyl optionally substituted with halogen, C1-C4-alkyl, -OH or C1-C4-alkoxy;

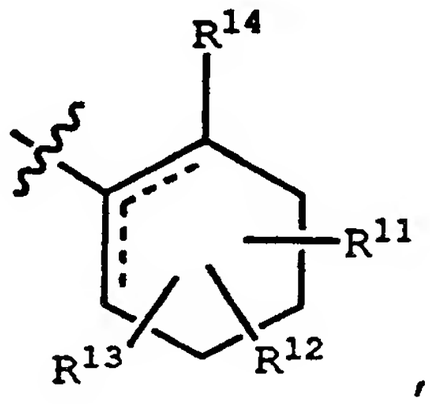
R^{10} is H, C1-C4-alkyl or benzyl;

X is saturated or unsaturated:

a)

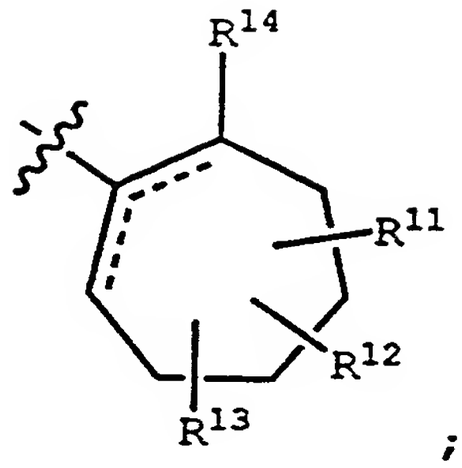


b)



, or

c)



;

R^{11} is

a) C1-C7-alkyl,

b) phenyl or phenyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-$S(O)_r$, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, and $-CO_2R^{10}$;

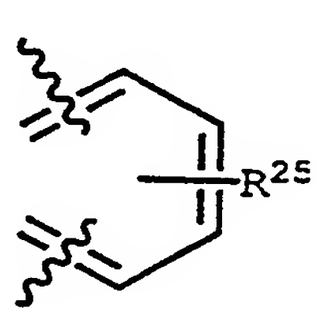
R^{12} and R^{13} are independently

a) H,

b) C2-C7-alkyl,

c) phenyl or phenyl optionally substituted with one or two substituents selected from the group consisting of halo (F, Cl, Br, I), C1-C4-alkyl, C1-C4-alkoxy, $-NO_2$, $-CF_3$, C1-C4-$S(O)_r$, -OH, $-NH_2$, -NH(C1-C4-alkyl), $-N(C1-C4-alkyl)_2$, $-CO_2R^{10}$;

R^{12} and R^{13} can be taken together when they are on adjacent carbon atoms to be



R^{14} is:

a) $-CO_2H$,

b) $-SO_2NHCO_2R^{24}$,

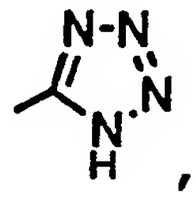
c) $-SO_2NHCOR^{24}$,

d) $-CONHSO_2R^{24}$,

e) $-SO_2NHCONHR^{24}$,

f) $-SO_2NHCSNHR^{24}$, or

g)



,

R^{15} is

a) H,

b) C1-C4-alkyl,

c) C3-C6-cycloalkyl,

d) aryl as defined above, or

e) -(C1-C4-alkyl)aryl,where aryl is as defined above;

R^{16} is

a) H,

b) C1-C6-alkyl,

c) aryl, as defined above,

d) -(C1-C4-alkyl)aryl, where aryl is as defined above, or

e) -(CH2)vCH(aryl)(aryl),where aryl is as defined above;

R^{17} is

a) H,

b) $-OR^{16}$, or

c) $-NR^{21}R^{22}$;

R^{18} and R^{19} are independently

a) H,

b) C1-C4-alkyl,

c) aryl as defined above, or

d) $-CH_2$aryl, where aryl is as defined above;

R^{20} is

a) H,

b) methyl, or

c) benzyl;

R^{21} and R^{22} are independently:

a) H,

b) C1-C4-alkyl,

c) aryl as defined above, or

d) -CH_2aryl, where aryl is as defined above,

or taken together comprise

e) -$(CH_2)_u$-, where u is 2 to 5, or

f) a morpholine ring;

R^{23} is

a) CF_3,

b) C1-C6-alkyl, or

c) phenyl;

R^{24} is

a) aryl as defined above,

b) C3-C7-cycloalkyl,

c) C1-C4-perfluoroalkyl,

d) C1-C10-alkyl optionally substituted with a substituent selected from the group consisting of:

i) aryl as defined above,

ii) heteroaryl, wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted 5- or 6-membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N, and S and wherein the substituents are members selected from the group consisting of -OH, -SH, C1-C4-alkyl, C1-C4-alkoxy, $-CF_3$, halo, $-NO_2$, $-CO_2R^{10}$, $-NH_2$, C1-C4-alkylamino, C1-C4-dialkylamino,

iii) -OH, -SH, C1-C4-alkyl, C1-C4-alkoxy, C1-C4-alkylthio, $-CF_3$, halo, $-NO_2$, $-CO_2R^{10}$, $-NH_2$, C1-C4-alkylamino, C1-C4-dialkylamino, $-PO_3H_2$;

e) heteroaryl as defined above;

R^{25} is

a) halo (F, Cl, Br, I),

b) C1-C4-alkyl,

c) C1-C4-alkoxy,

d) $-NO_2$,

e) $-CF_3$,

f) C1-C4-$S(O)_r$,

g) -OH,

h) $-NH_2$,

i) -NH(C1-C4-alkyl),

j) $-N(C1-C4-alkyl)_2$,

k) $-CO_2R^{10}$, or

l) H;

m is 0 to 2;

r is 1 to 2;

u is 2 to 5;

w is 1 to 2v+1;

and, the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein

R^1 is H;

R5 is:

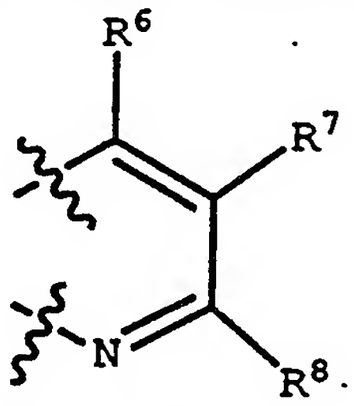
a) $-(CH_2)_mCHR^{15}OR^{16}$,

b) $-COR^{17}$,

c) $-(CH_2)_mCHR^{15}COR^{17}$, or

d) $-CONHSO_2R^9$;

or R^4 and R^5 taken together are



R^6, R^7, R^8 are independently:

a) H,

b) C1-C4-alkyl

c) halo,

d) $-CF_3$

e) $-N(R^{20})_2$,

h) $-CO_2R^{16}$

i) $-CONHSO_2R^9$, or

j) tetrazol-5-yl;

R^{24} is

a) aryl as defined in claim 1,

b) C3-C7-cycloalkyl,

c) .C1-C4-perfluoroalkyl,

d) C1-C10-alkyl optionally substituted with phenyl.

3. A compound of Claim 2 selected from the group consisting of:

- 1-[[4-(2-carboxy-4-phenylcyclohexen-1-yl)phenyl]methyl]-4-chloro-5-hydroxymethyl-2-propylimidazole

- 1-[[4-[2-carboxy-4-(1,1-dimethylethyl)cyclohexen-1-yl]phenyl]methyl]-4-chloro-5-hydroxymethyl-2-propylimidazole

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-4-phenylcyclohexen-1- yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-4,4-diphenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-4-propylcyclohexen-1 -yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 5,7-dimethyl-2-ethyl-3-[[4-[2-carboxy-3-phenylcyclohexen-1 -yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 1-[[4-[2-carboxy-4-(1,1-dimethylethyl)cyclohexen-1-yl]phenyl]methyl]-4-ethyl-2-propylimidazole-5-carboxaldehyde

- 5,7-dimethyl-2-ethyl-3-[[4-[2-(1-H-tetrazol-5-yl)-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

- 1-[[4-[2-(1H-tetrazol-5-yl)-4-(1,1-dimethylethyl)cyclohexen-1-yl]phenyl]methyl]-4-ethyl-2-propylimidazole-5-carboxaldehyde

- 5,7-dimethyl-2-ethyl-3-[[4-[2-[[(butoxycarbonyl)amino]sulfonyl]-4-phenylcyclohexen-1-yl]phenyl]methyl]-3H-imidazo[4,5-b]pyridine

4. A compound as claimed in claim 1 as specified in any one of Examples 1 to 50.

5. A compound of any one of claims 1 to 4 for use in a method of treatment of the human or animal body by therapy or diagnosis.

6. A pharmaceutical composition comprising a pharmaceutically suitable carrier and a compound of any one of claims 1 to 5.

7. Use of a compound as claimed in any one of claims 1 to 4 in the manufacture of a medicament for use in treating hypertension in a warm blooded animal.

8. Use of a compound as claimed in any one of claims 1 to 4 in the manufacture of a medicament for use in treating congestive heart failure in a warm blooded animal.

Patents Act 1977 **Examiner's report to the Comptroller under Section 17** **(The Search report)**	Application number GB 9324606.4
Relevant Technical Fields (i) UK Cl (Ed.L) (ii) Int Cl (Ed.5) C07D 233/54, C07D 471/04	Search Examiner DIANE DAVIES Date of completion of Search 26 JANUARY 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: CAS-ONLINE, EDOC	Documents considered relevant following a search in respect of Claims :- 1-8

Categories of documents

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A: Document indicating technological background and/or state of the art.

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E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	DE 4032522 A (SCHERING AG) compounds of formula 1 where R is the first formula on page 3 line 40	
A	J Med. Chem., 35(14), 2658-67, (1992), Ho-Shen Lin et al "Nonpeptide Angiotensin II Receptor Agonists: Synthetic and computational Chemistry of N-[[4-[2-(2H-tetrazol-5-yl) -1-cycloalken-1-yl]phenyl]menthyl]imidazole Derivitives and Their In Vitro Activity"	
A,P	J. Chinese Chem. Soc., 40, 273-82 (1993), Ho-Shen Lin et al, "Synthesis and In Vitro evaluation of N-[[4-[2-(carboxyl0-1 -cycloalken-1-yl]phenyl]methyl]imidazoles as Non-peptide Angiotensin II Receptor Antagonists"	

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).